VOLUME 16 NUMBER 2

THE ARCHIVES

OF

INTERNAL MEDICINE

AUGUST 15, 1915

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

ENTERED AS SECOND-CLASS MATTER, JANUARY 23, 1908, AT THE POSTOFFICE AT CHICAGO, ILLINOIS, UNDER ACT OF CONGRESS OF MARCH 3, 1879

CONTENTS OF VOLUME XVI

JULY, 1915. NUMBER 1

The Archives of Internal Medicine

VOL. XVI. AUGUST, 1915 No. 2

AN ATTEMPT TO DETERMINE THE DIAGNOSTIC IMPORTANCE OF HEAD'S ZONES OF HYPERALGESIA *

LOVELL LANGSTROTH, M.D.
SAN FRANCISCO

The following work is an attempt to estimate the practical importance of cutaneous hyperalgesia in the diagnosis of visceral disease.

Ross[1] published, in 1887, an article on the segmental distribution of sensory disorders. He first took up the distribution of the sensory nerves and showed that in man it is somewhat similar to that in the primitive vertebrates except for some disarrangement caused by the development of the limbs. In the primitive vertebrate each segment of the cord supplies an area of the body surface immediately over it and the viscera under this area. In man the relation of the viscera to the body surface has so changed that the somatic segment and the viscus supplied by the same cord segment are no longer one over the other. Pain, he said, might be splanchnic or somatic, splanchnic pain being vaguely felt over the region of the diseased organ causing it, somatic pain being felt in the sensory nerves derived from the corresponding cord segment. He then gave briefly the distribution of the somatic pain for each viscus and named the dorsal segments through which the stimuli from the splanchnic nerves are diffused to the somatic nerves.

The following tabular outline gives the segmental supply of each organ, the location of the referred pain, and the other symptoms associated through the same nerve supply, according to Ross.

Stomach: Dorsal 4, 5, 6—pain between the shoulders and in front of the chest; oppression or constriction in the left side (spasm of intercostals) brow-ache (pneumogastric).

Lungs: Cranial, 10 dorsal (?)—pain at midsternum and between the shoulders; palpitation; gastric disorders; rumbling of the bowels.

Pleura: Cervical 4 (phrenic)—pain over outer tip of clavicle; otherwise directly over seat of disease.

Heart: Dorsal 2 diffusing to dorsal 1, 3, 4 and cervical 8—pain in left chest and between the shoulder blades and down inside of left arm.

Liver: Dorsal 7, 8—pain at angle of scapula.

Bowels: Dorsal 10, 11—pain in the back and in front about the umbilicus.

Kidneys: Somatic and splanchnic pain coincide.

* Submitted for publication March 3, 1915.

1. Ross, James: On the Segmental Distribution of Sensory Disorders, Brain, 1888, x, 333.

Pelvis and Ureter: Lumbar 1, 2—pain down inside of thigh along ileoinguinal and genitocrural and external cutaneous nerves.

Testicle: Lumbar 1—dragging pain in loin; ileoinguinal nerve.

Ovary: Lumbar 1, 2, 3—pain above iliac crests posteriorly (posterior branches of second lumbar); above the groins (ileoinguinal), and in iliac region and the hip-joints.

Bladder: Sacral 3—pain along urethra to tip of penis (pudic nerve).

Rectum: Sacral 3—pain in urethra (pudic) and down back of thigh (small sciatic).

Uterus: Sacral 2, 3, 4—pain over lower sacrum. Os uteri: Sacral 3—coccygeal neuralgia.

Mackenzie[2] published his first work on sensory symptoms in visceral disease in 1892. He noted the site of the pain in diseases of the various organs and found that frequently it did not correspond with the situation of the viscus involved but was approximately constant in location for a given organ, and was often accompanied by tenderness of the spines of certain vertebrae and by hyperalgesia of the skin over the site of the pain. He made no attempt to connect the viscera with definite spinal segments but mapped out roughly the skin areas involved in the pain. The following tabular outline shows the site of the referred pain in diseases of the various organs according to Mackenzie.

Heart: Pain over midsternum from right of midline to beyond the left nipple line or under the left breast, down the left arm, between the shoulder blades; occasional hyperalgesia. (Note agreement with Ross.)

Lungs: No referred pain; pain when present due to accompanying pleurisy which is localized to site of disease. (Compare Ross.)

Esophagus: Pain over lower sternum.

Stomach: Pain in upper epigastrium; tenderness in epigastrium and to left over sixth, seventh and eighth interspaces. (Note disagreement with Ross.)

Small intestine: Pain on either side of umbilicus. (In agreement with Ross.)

Large intestine: Pain midway between umbilicus and symphysis.

Rectum: Pain over upper sacrum. (In disagreeement with Ross.)

Uterus: Pain over upper sacrum. (In agreement with Ross.)

Uterine contraction: Pain in midline above symphysis.

Liver: No pain. (Compare Ross.)

Gall passages: Pain in midline or a little to right at level of lower epigastric and upper umbilical areas. Hyperalgesia frequent.

Kidney: No pain. (In disagreement with Ross.)

Pelvis and ureter: Pain from above middle of iliac crest in lumbar region downward and inward to region of penis or scrotum. (In disagreement with Ross.)

Bladder: Pain along urethra or under surface of penis to tip of penis.

It will be seen by comparing the two outlines that Mackenzie and Ross disagree frequently as to the site of the referred pain.

Mackenzie concluded that the pain of visceral organs was entirely an associated pain due to stimulation of the spinal centers of sensory nerves.

---

2. Mackenzie, James: Sensory Symptoms Associated with Visceral Disease, Med. Chron., 1892, xvi, 293.

Head, following the work suggested by Ross, gave the first results of his work[3] on the disturbances of sensation in visceral disease in 1893. He recognized definite areas of hyperalgesia in connection with symptoms or signs of irritation of certain viscera and found in addition certain maxima in those areas where the hyperalgesia was greatest and which might be present alone. Following the idea that herpes zoster was inflammation of the posterior roots,[4] he carefully worked out the areas of distribution of a large number of cases of this disease and

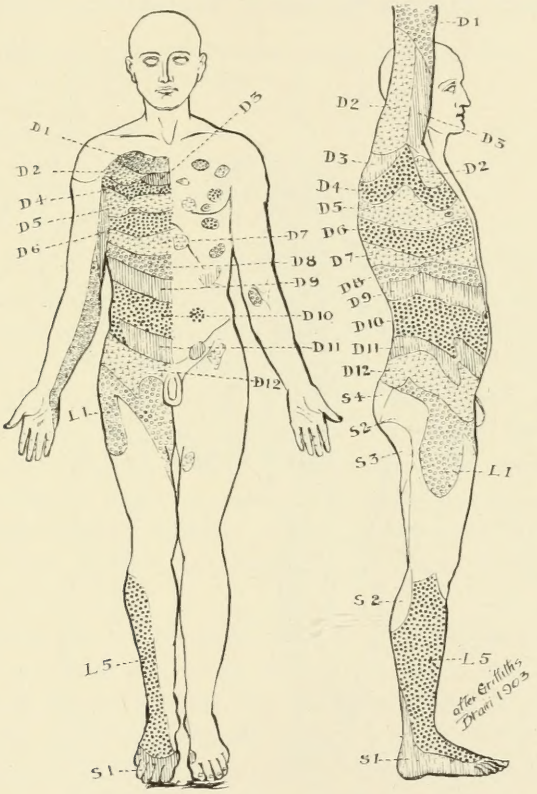


Fig. 1.—Head's zones of hyperalgesia.

found that they agreed with the hyperalgesic areas mapped out in visceral disease, in that they did not overlap, had the same distribution, and the same maxima. Thus he was able to argue that his hyperalgesic areas represented a disturbance set up in different cord segments by afferent visceral impulses. Beginning at the second rib he found thir-

3. Head, Henry: On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease, Brain, 1893, xvi, 1.

4. Von Bärensprung: Ann. d. Charité, Krankenhaus zu Berlin, 1861, ix, 2, p. 40; 1862, x, 1, p. 37; 1863, xi, 2, p. 96.

teen areas which fitted into one another. The upper borders of certain ones he was able to identify as belonging to certain spinal segments by comparison with the upper border of analgesia in a few organic lesions. The first area beginning at the second rib was found to represent the first dorsal segment. The sequence was then uninterrupted down to the first lumbar segment inclusive. The second, third and fourth lumbar segments were found not to be affected in visceral disease and to form a "gap." The fifth lumbar and four sacral segments were represented by five additional areas. A similar

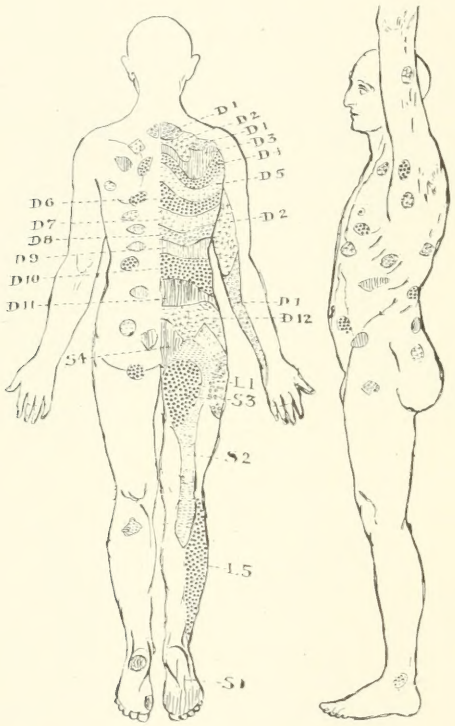


Fig. 2.—Head's zones of hyperalgesia.

"gap" was formed by the fifth, sixth, seventh and eighth cervical segments. The distribution of the cutaneous pain fibers from those segments not affected in visceral disease was determined by organic lesions of the cord and by herpetic eruptions. Thus the whole of the body and limbs was mapped out into areas, each of which represented the cutaneous distribution of the pain fibers given off from one segment of the cord (Figs. 1 and 2).

The following classification taken from Head's article shows the segments receiving fibers from the different viscera.

Heart: Dorsal 1, 2, 3—cervical plexus (depressor?).
Lungs: Dorsal 1, 2, 3, 4, 5—cervical plexus (vagus?).
Stomach: Dorsal 6, 7, 8, 9—cardiac end, 6, 7, pyloric end, 9.
Intestines: (*A*) down to upper part of rectum, dorsal 9, 10, 11, 12. (*B*) rectum, sacral 2, 3, 4.
Liver and Gallbladder: Dorsal 7, 8, 9, 10 (6?).
Kidney and Ureter: Dorsal 10, 11, 12. The nearer the lesion lies to the kidney the more is the pain and tenderness associated with the dorsal 10. The lower the lesion in the ureter the more does the lumbar 1 tend to appear.
Bladder: (*A*) Mucous membrane and neck sacral (1)—2, 3, 4.
(*B*) Overdistention and ineffectual contraction, dorsal 11, 12, lumbar 1.
Prostate: Dorsal 10, 11—(12), lumbar 1—sacral 1, 2 and 3.
Epididymis: Dorsal 11, 12, lumbar 1.
Testis: Dorsal 10.
Ovary: Dorsal 10.
Appendages: Dorsal 11, 12, lumbar 1.
Uterus: (*A*) In contraction, dorsal 10, 11, 12, lumbar 1.
(*B*) Os uteri, sacral (1), 2, 3, 4, (lumbar 5).

Head found that there was a tendency for the pain and tenderness caused by visceral disease to spread to other areas and that this spread followed general laws. Frequently they became bilateral or involved areas, having no connection with the affected organs. Certain areas were more easily affected in this manner than others, as the tenth dorsal or the sixth dorsal in women, and the seventh dorsal in men. Anemia, fever or mental trouble, were found to be frequent causes for generalization in which at times the maxima of many areas were affected. Some cases of hysteria of the cerebrospinal type had areas of analgesia with borders corresponding to those of the segmental areas.

He regarded the reference of pain in visceral disease as of the same nature as allochiria. The viscera having a lesser degree of sensibility than the surface of the body and being in close central connection with it, the afferent pain stimuli are accepted by a psychical error as coming from the area into which they are diffused. Though insisting so strongly on the reference of pain to the body surface, he believed that visceral pain was also referred to the organs affected, being there of a dull, aching character instead of a sharp, stabbing character.

Hyperalgesia of the skin in disease of the underlying viscera he explained by the exaggeration of the afferent sensory skin stimuli in the cord segment which had been disturbed by the abnormal visceral stimuli. He never found hyperesthesia as a result of visceral disease and concluded that the central paths of the pain fibers from the skin and viscera were closely connected.

In 1893, Mackenzie's[5] second paper emphasized several points on which his work was found to conflict with that of Head. After the appearance of Head's first work, Mackenzie again carefully observed a number of cases in which he found hyperalgesia in visceral disease and a number of cases of herpes zoster, but found that he could not make the areas agree with those of Head.

In a second paper[6] Head took up the subject of referred pain in the head and neck. As no attempt was made in the present investigation to determine areas of hyperalgesia above the trunk, this portion will be very briefly discussed. He attempted to show that such organs as the nose, the eye, the ear, the teeth, the tongue, the salivary and other glands, the tonsil, the larynx and the brain, stood in relation with cutaneous areas of the head and neck to which pain was referred in diseases of these organs. Herpetic eruptions over the head and neck were found to occur over these same areas. He found that headaches accompanying disease of the thoracic or abdominal viscera were accompanied by hyperalgesia of head areas, and that the latter were always located with reference to the dorsal or other area involved. Thus the situation of a headache in cardiac disease was determined by the dorsal segment affected. He carefully worked out the distribution of the pain fibers in the branches of the fifth cranial nerve, and showed that they did not correspond with his areas.

In a third paper[7] he took up diseases of the heart and lungs and showed the groups of areas affected in various pathologic conditions. Here, as before, he admitted the presence of local pain and of deep tenderness in both diseases of the heart itself, and of the pericardium, as distinguished from referred pain and superficial tenderness.

He found that with an aortic murmur, pain was liable to be referred to the second, third and fourth dorsal, and sometimes to the third and fourth cervical areas. When a systolic murmur at the apex was also present, or when it developed, pain was no longer referred. In aneurysms of the aorta, pain was referred according to the situation of the dilatation as follows: ascending aorta, to the third and fourth cervical, first, second, third and occasionally fourth dorsal, usually of the left, but also of the right side; arch of aorta to the inferior laryngeal area of both sides; descending aorta to the sixth, seventh and eighth dorsal areas. Simple mitral regurgitation, or cases with a mitral murmur obliterating the first sound, and with a diastolic

5. Mackenzie, James: Some Points Bearing on the Association of Sensory Disorders and Visceral Disease, Brain, 1893, xvi, 321.

6. Head, Henry: On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease. Part II, Brain, 1894, xvii, 339.

7. Head, Henry: On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease. Part III, Brain, 1896, xix, 153.

murmur, were found not to have pain. With a mitral systolic murmur, a sharp first sound at the apex, and usually a presystolic or diastolic murmur, pain was referred to the fifth, sixth, seventh, eighth and occasionally to the ninth, dorsal areas. In distention of the liver produced by right-heart failure, pain was referred to the eighth, ninth and tenth dorsal areas. In paroxysmal cardiac pain, or angina pectoris, the referred pain was widespread and involved practically all the cardiac segments.

He found the most important considerations for the production of referred pain to be: "firstly the maintenance of considerable tension within a cavity of the heart, accompanied by, secondly, a sudden accession of tension (owing to regurgitation) at the moment when the walls of the cavity are dilating after systole." Thus, in aortic stenosis the tension in the ventricle is high, and if there be a coincident regurgitation at the aortic valve, then during diastole there is a rush of blood back into the ventricle at a comparatively high tension and the conditions for referred pain are present. Similar reasoning applies to mitral stenosis in its early and middle stages. From the above considerations he tabulated the sensory supply of the heart and aorta as follows:

Transverse arch of aorta: Inferior laryngeal segment.
Ascending arch of aorta: Cervical 3, 4, dorsal 1, 2, 3, (4).
Ventricle: Dorsal 2, 3, 4, 5 (6?).
Auricle: Dorsal 5, 6, 7, 8 (9?).

He showed that this sensory supply agreed quite well with the embryologic development of the various chambers of the heart.

Pain in connection with disease of the lungs was found to be either local or referred. The pain of pleurisy coincided precisely with the situation of the area of pleura involved and was accompanied by deep tenderness but not by superficial hyperalgesia.

Referred pain was found most frequently in those cases of phthisis in which the progress of the disease was marked by successive bronchitic attacks in which previously healthy lung tissue was involved. This he thought was due to the fact that the end organs of the sensory nerves in the portion of the lung under invasion were still intact and capable of being irritated and conveying impressions. With the disease well advanced, the nerve endings were destroyed and that portion of the lung was no longer able to cause referred pain. He found referred pain and superficial tenderness particularly liable to "spreading," and attributed this to the cachexia and the rise in temperature by which each advance of the disease was accompanied. Very roughly he was able to estimate the portion of the lung under invasion by the cutaneous areas involved in the hyperalgesia. The innervation of the

lung was found to be as follows: Lungs: cervical 3, 4; dorsal 3, 4, 5, 6, 7, 8, 9.

In 1900,[8] Head published the results of a number of necropsies in cases of herpes zoster, showed that the disease was accompanied by an inflammatory process of the posterior root ganglion and in general substantiated his previously worked out areas for each spinal segment.

In 1901,[9] he followed this by work which attempted to show that psychical states in visceral disease were connected with the hyperalgesic areas on the head and neck which were found in conjunction with involvement of certain spinal segments. Thus a patient with double aortic disease had widespread referred pain and tenderness over the left side of the thorax, headache and scalp tenderness over the forehead and temple, and hallucinations of sight, depression and suspicion.

In 1912[10] Mackenzie reviewed and elaborated the whole subject of referred pain and tenderness. He believed that all visceral pain was referred and gave experimental evidence to show that the viscera were absolutely insensitive to all ordinary forms of stimulation. The muscles and subperitoneal tissue, as well as the skin, he found became hyperalgesic when the corresponding cord segment became irritable from visceral disease; and muscle spasm over the diseased organ originated in the same segment. Cutaneous hyperalgesia he found comparatively rare; and when present he was unable to find that the areas involved fitted those worked out by Head.

Experimental work by Hertz[11] throws grave doubts on the referred character of all pain, at least in disease of the alimentary tract. He showed that the stomach was indeed insensitive to ordinary stimuli but that sensations of pain were caused on distention of this organ. This he was able to prove by inserting inflatable rubber bags into the stomach. When distention was caused at a certain level of the esophagus the patient was able, fairly accurately, to locate the level of the painful stimuli, and the cutaneous surfaces over both front and back of the thorax were not found hyperalgesic. Thus he concluded that pain in disease of the alimentary tract was caused by distention of the circular fibers of the muscular coat and that the sensory nerves of the sympathetic system became sensitive to this distention and

8. Head, Henry, and Campbell, A. W.: The Pathology of Herpes Zoster and Its Bearing on Sensory Localization, Brain, 1900, xxiii, 353.

9. Head, Henry: Certain Mental Changes that Accompany Visceral Disease, Brain, 1901, xxiv, 345.

10. Mackenzie, James: Symptoms and Their Interpretation, 1912. London: Shaw & Sons.

11. Hertz: The Sensibility of the Alimentary Canal. London, 1911: Oxford University Press, pp. 50-52.

expressed it as pain which was referred to the place usually occupied by the viscus according to the law of average localization. Such distention is caused when forceful peristalsis meets such an obstruction as a spastic pylorus, almost separates the pyloric antrum from the remainder of the stomach by a circular wave of constriction and raises the tension of the portion beyond the advancing constricting ring.

T. C. Noeggerath and von Salle[12] in a study of early tuberculous lesions in children, found that of forty-six patients, of whom twenty-four were clinically suspected of tuberculosis, "Head's zones" could be demonstrated in sixteen, or 66 per cent. Hyperalgesia was not found in children without lung signs. The areas found involved were the fourth cervical and second, third and fourth dorsal.

The work of Head was brought to mind by a case of aneurysm of the aorta in which there was severe pain and hyperalgesia of the skin corresponding almost exactly with the diagrams of Head. It was then determined to examine a large series of ward patients for hyperalgesia in order to determine the frequency of its occurrence and estimate, if possible, its importance in diagnosis. The investigation covered a period from July 1, 1913, to July 1, 1914, during which 460 patients were examined. Hyperalgesia was found as a rule somewhat indefinite, inconstant and difficult to elicit. In no case was it so marked that the head of the pin was mistaken for the point. Doubtless errors have been made, but they were unavoidable in these patients, many of whom were of a low grade of intelligence and too ill to pay much attention to a long examination.

Laryngitis, acute: 2 cases showed no hyperalgesia.

Bronchitis, acute: 6 cases. Of these one was almost in uremic coma on admission so that the bronchitis was a postmortem finding, and in another there was a possibility of tuberculosis. Three of this group complained of pain but none showed hyperalgesia.

Chronic bronchitis: 12 cases. Pain was not a feature except in one case, and this patient had no hyperalgesia.

Infarct of lung: 3 cases; in two the infarcts were postmortem findings. The patient in Case 143 had severe pain and a localized friction rub without hyperalgesia.

Abscess of lung: 4 cases; one patient complained of pain; none showed hyperalgesia.

Bronchopneumonia, in 12 cases, was terminal or a postmortem finding in eleven. One patient, Case 264, complained of discomfort in the epigastrium but not of pain. He was a diabetic who died three

12. Head's Zones in Early Tuberculosis of Childhood, Jahrb. f. Kinderheilk, 1911, xxiv, No. 74, reviewed by Michael, Am. Jour. Dis. Child., 1912, iii, 186.

days after admission to the hospital. A small area of hyperalgesia was found (see Fig. 3) corresponding approximately to one of the maxima of the eighth dorsal area. This would indicate, according to Head, disturbance in the heart, lungs, stomach, or the liver and gall passages. At necropsy he was found to have a healed chronic suppurative pleurisy of the right base, tuberculosis of the lungs healed at the base, healed pneumonia of the left lung with carnification at the base, recent pneumonia, and an acute gastro-enteritis.

In 2 cases of lobar pneumonia both patients had pain in the chest, but hyperalgesia was not found.

Of tuberculosis of lungs there were 38 cases. Head found that pain was a more frequent feature of this disease during bronchitic

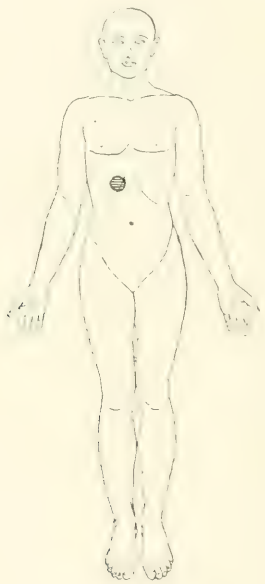


Fig. 3.—Conditions noted in Case 264; hyperalgesia found in broncho-pneumonia. A maximum of the eighth dorsal area was involved.

attacks which marked the spread of the disease. On account of the short period of time that these patients were allowed to remain in the hospital, the opportunity was not found to determine definitely when new involvement occurred. Furthermore, on account of the unreliability of the patient's statements as to the duration of his symptoms, it was often not possible during the short period of observation to determine whether the disease was acute or chronic. In a large majority of the cases, the disease was well advanced, frequently it was far advanced. In only 11 cases was the probable duration under two years. Seventeen patients complained of pain which seemed connected

with their lung infection. Of these only 5 were probably fairly acute cases. Of the 17 patients complaining of pain, evidence of pleurisy was found in nine, the pain was abdominal in two, precordial and accompanied by palpitation in one, and in the arms in one. Thus only three cases in this group had pain without evidence of pleurisy. Hyperalgesia was found in Case 84. This patient, aged 39, had had cough, fever, chest pain and hemoptysis for three months at 22, and cough, expectoration and some night sweats at times to date of admission. During the last five months of this period he had had pain in the back, chest, and arms, increased by movement. Examination showed evidence of a thickened pleura, some infiltration and adhesions over the lower half of the left lung, and slight changes throughout.

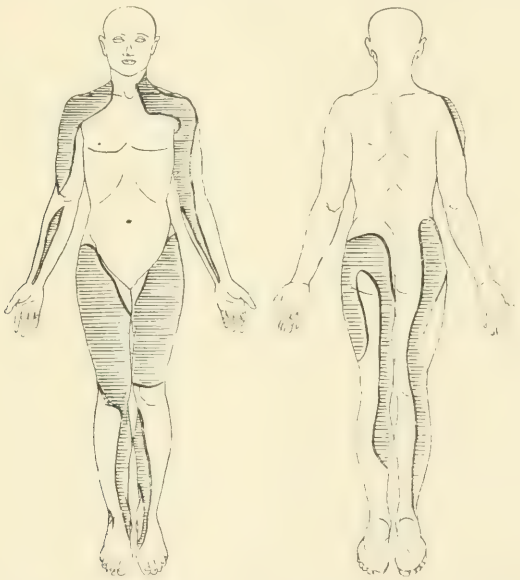


Fig. 4.—Conditions noted in Case 84; hyperalgesia in tuberculosis of the lungs. Portions of the first, third and twelfth dorsal, first and fifth lumbar, and first, second and third sacral areas were involved.

The sputum was occasionally blood tinged but no tubercle bacilli were found. There was hyperalgesia as shown in Figure 4, corresponding to portions of the first, third and twelfth dorsal, first and fifth lumbar and first, second and third sacral areas, but to an equally great extent to areas into which visceral pain is not referred, according to Head. Involvement of the first and third dorsal would indicate disease of the heart or lungs; of the twelfth dorsal and first lumbar, disturbance of the kidney and ureter, bladder or epididymis, none of which were found. Involvement of the first lumbar, first, second and third sacral areas would indicate disease of the prostate which was apparently

normal. Disease of the vertebrae was not found. It is evident that in this case the hyperalgesia cannot be accepted as an indication of visceral disturbance unless its wide extent to areas not usually affected by visceral disease be accounted for by "spreading."

Six (chronic adhesive) out of 37 cases of pleurisy were found only at necropsy, eleven were apparently healed or of long standing, eleven were acute, eight were serofibrinous and one was demonstrated tuberculosis.

In chronic pleurisy, 11 cases, one patient complained of pain which seemed connected with the lesion. Hyperalgesia was not found in this group.

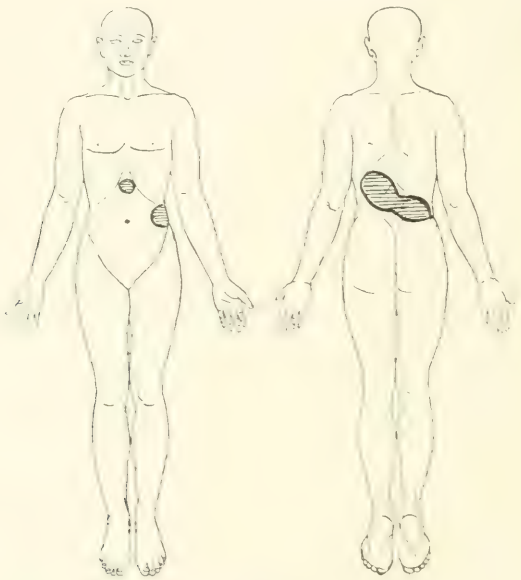


Fig. 5.—Conditions noted in Case 287; hyperalgesia in serofibrinous pleurisy. The maxima of the seventh dorsal areas and portions of the ninth, tenth and eleventh dorsal areas were involved.

In acute fibrinous pleurisy, 11 cases, the pleurisy was terminal in two; in another the lesion was small and probably due to an infarct. The remaining eight patients complained of pain. Hyperalgesia was not found.

In serofibrinous pleurisy, 8 cases, pain was a feature in every case and was more severe and constant than in the preceding group. Hyperalgesia was found in Case 287. This patient gave a history of general indisposition for a year, followed three weeks before admission by pain in the left chest and back, steadily increasing in intensity, until he felt dizzy and unable to work. Examination showed signs of fluid in the left chest, the heart displaced to within 1 cm. of the right nipple line,

the liver and spleen enlarged and palpable, the latter tender, and hyperalgesic, as shown in Figure 5, corresponding approximately with the maxima of the seventh dorsal area anteriorly, and portions of the ninth, tenth and eleventh dorsal areas laterally and posteriorly. The pain was apparently due to pressure on the various organs in close proximity, as the pleural surfaces were separated by about 4,000 c.c. of fluid. Involvement of the seventh dorsal might come either from the heart or lung, both of which were under great pressure. No explanation was found for the involvement of the other areas.

There was one case of tuberculosis of the pleura. Patient 108 had had palpitation and shortness of breath, precordial pain, cough, loss of weight, and night sweats, for five months before admission. The left

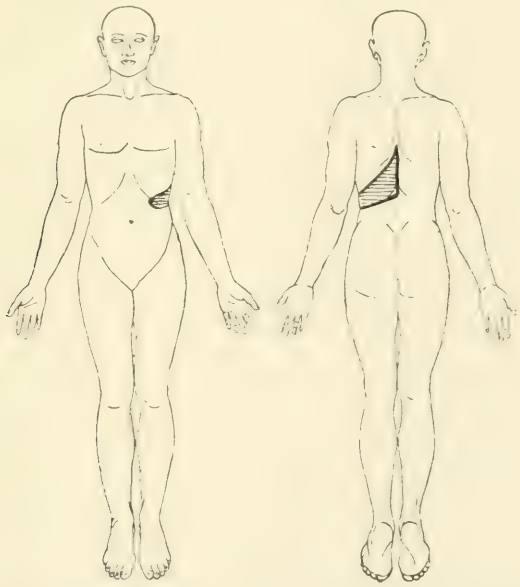


Fig. 6.—Conditions noted in Case 108; hyperalgesia in tuberculous pleurisy. Portions of the seventh, eighth and ninth dorsal areas were involved.

pleura contained a large amount of fluid, the heart was displaced as far as the right anterior axillary line, and the urine contained a heavy cloud of albumin, hyaline and granular casts. Tubercle bacilli were demonstrated in the pleural fluid. The Wassermann reaction was $++-$ in the blood. Hyperalgesia was found as shown in Figure 6, corresponding anteriorly with a portion of the ninth dorsal area, posteriorly with portions of the seventh, eighth and ninth dorsal areas. The hyperalgesia seems to follow quite definitely the course of the intercostal nerves instead of agreeing with one or more segmental areas. Here as in the previous case it seems impossible to say whether

the site of the disturbance is in the heart or the lung. Thus, in 116 cases of disease of the larynx, bronchi, lungs and pleura, 30, or 25.8 per cent., complained of pain, and of these, 4, or 13 per cent., showed hyperalgesia which seemed very doubtfully connected with the respiratory system.

Of 40 cases of valvular disease of the heart two were classed as acute endocarditis and were without pain. Six were classed as subacute endocarditis and two patients of this group complained of pain. There were thirty-two classed as chronic endocarditis or chronic valvular disease, and eleven patients of this group complained of pain which seemed connected with the heart.

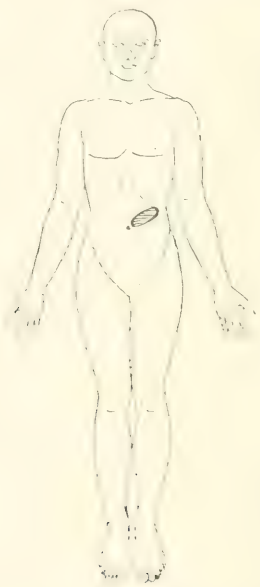


Fig. 7.—Conditions noted in Case 188; hyperalgesia in mitral insufficiency. One of the maxima of the ninth dorsal area was involved.

Head found that the lesions most favorable for the production of cardiac pain were aortic regurgitation (without mitralization) and mitral stenosis in its early and middle stages. The cases have therefore been grouped according to lesions.

Aortic insufficiency: 11 cases; six of these patients had pain. Hyperalgesia was found in one case but involved one leg only and was apparently due to a spondylitis.

Mitral insufficiency: 17 cases; five patients in this group had pain. One, Case 188, showed hyperalgesia. This patient, aged 67, gave a history of early scarlet fever, rheumatism and sore throat. Three years before admission, he developed a chronic cough and later sore-

ness under the sternum and over the upper abdomen and occasional pain down the left arm. Examination showed a chronic bronchitis with emphysema, a moderately enlarged heart, with a mitral murmur, some edema of the lungs, an enlarged and tender liver, edema of the legs and general arteriosclerosis. There was hyperalgesia as shown in Figure 7, corresponding approximately with one of the maxima of the ninth dorsal area. Here, as in other cases, it is impossible to say whether the disturbance in this segment was due to distention of one of the chambers of the heart, slight infection of the lungs or to enlargement of the liver.

Mitral stenosis: 10 cases; two patients in this group complained of pain, and one had hyperalgesia. This patient, Case 227, a man of 27,

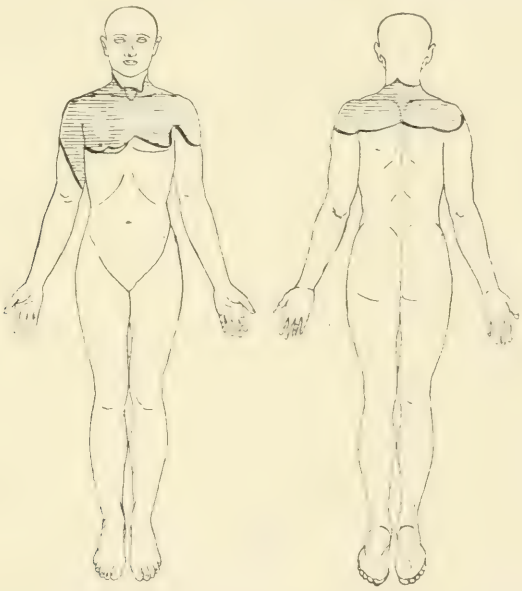


Fig. 8.—Conditions noted in Case 227; hyperalgesia in mitral stenosis. The inferior laryngeal, sternomastoid, sternonuchal, and first, second and third dorsal areas were involved.

had a history of previous sore throat, and joint infections following and possibly due to gonorrhea. He had had precordial pain, dyspnea and palpitation, and finally, several years before admission, stiffness of most of his joints, including his spine, with pain on movement. Examination showed pyorrhea, a mitral lesion with slight stenosis, slight hyperthyroidism, a palpable spleen, periarticular thickening about many of the joints, particularly of the ankles and knees, and extreme rigidity and considerable kyphosis of the dorsal and cervical spine. There was hyperalgesia as shown in Figure 8, involving the inferior laryngeal, sternomastoid, sternonuchal, and first, second and

third dorsal areas. This hyperalgesia corresponded to the area over which pain was felt on motion of the spine. This fact, with the evident spondylitis, makes it seem possible that the hyperalgesia was due not alone to the cardiac condition but to the superposition of afferent cardiac pain impulses on centers already made irritable by the spondylitis.

Syphilis of aorta and aortic valves: 7 cases; three of these patients had pain; hyperalgesia was not found.

Arteriosclerosis of aorta and aortic valves: 3 cases; one patient in this group had pain; hyperalgesia was not found.

Arteriosclerosis of coronary arteries: 1 case (demonstrated at postmortem); this patient had attacks of stabbing precordial pain without hyperalgesia.

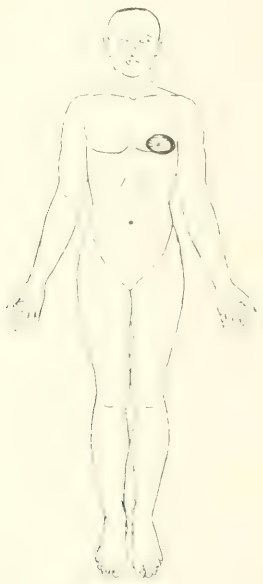


Fig. 9.—Conditions noted in Case 139; hyperalgesia found in a case of angina pectoris. The maxima of the fourth, fifth and sixth dorsal areas were involved.

Angina pectoris: 2 cases; one, Case 139, showed hyperalgesia. This patient gave a history of attacks of knife-like pain over the heart dating back eight years and accompanied for two years by a feeling of constriction about the chest, a sense of impending death, choking, and an irregular pulse. Examination showed an enlarged heart, auricular and ventricular extrasystoles and cutaneous hyperalgesia as shown in Figure 9, corresponding to the maxima of the fourth, fifth and sixth dorsal areas, all of which may be affected in diseases of the heart.

Aneurysm of aorta: 2 cases; both these patients had pain while only one had hyperalgesia. This patient, Case 206, had a history of cough, expectoration, pain in the chest, and headache for four months. Examination showed a large aneurysm of the arch of the aorta which apparently was not in contact with the chest wall or the bodies of the vertebrae and hyperalgesia as shown in Figure 10, corresponding to the maxima of the seventh, eighth and ninth dorsal and the sternomastoid area. The dorsal hyperalgesia had no connection with the aneurysm and remained unexplained.

Myocarditis: 25 cases; in this group were placed those patients having signs and symptoms of myocardial insufficiency without evi-

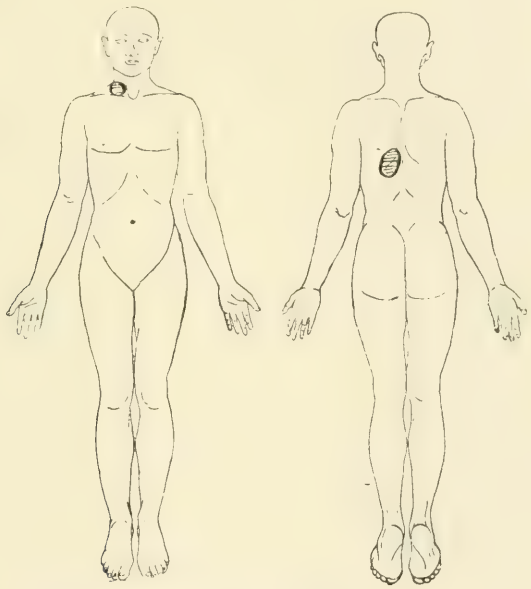


Fig. 10.—Conditions noted in Case 206; hyperalgesia found in a case of aneurysm of the aorta. The maxima of the seventh, eighth and ninth dorsal and the sternomastoid areas were involved.

dence of a valvular lesion. Nine patients complained of pain which in four cases was in the epigastrium and probably due to enlargement of the liver. Hyperalgesia was not found.

Chronic pericarditis: 3 cases; one was not found till necropsy. Two others both had pain and hyperalgesia. Patient in case 352 gave a history of slight pain in the chest at times for two years. Ten days before admission this increased so that it hurt him to breathe and was accompanied by fever, malaise, weakness, and loss of weight. Examination showed slightly cyanotic lips, a low pitched friction sound at the apex in mid diastole, a temperature of 101, a pulse of 100, and

30 respirations to the minute. While in the hospital he developed very severe pain and oppression in the chest. Hyperalgesia was found as shown in Figure 11, corresponding to the maxima of the fourth dorsal area, which according to Head would suggest the ascending arch of the aorta, the ventricle, or the lungs. All of these viscera were normal so far as could be determined. Head found that the pain in inflammation of the pericardium was purely local and accompanied by deep tenderness, a view with which the facts of the case just described do not agree. Patient 24 had had an illness about nine months before characterized by shortness of breath, chills and fever. After that he found himself unable to work without pain in his chest. There was

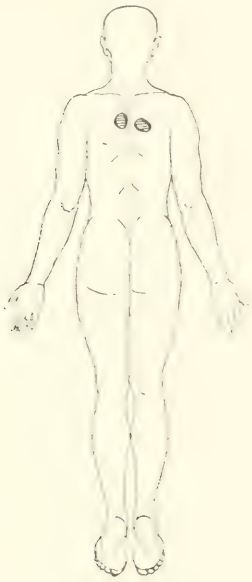


Figure 11

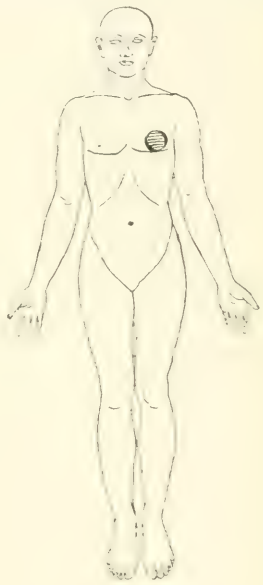


Figure 12

Fig. 11.—Conditions noted in Case 352; hyperalgesia in a case of pericarditis, The maxima of the fourth dorsal areas were involved.

Fig. 12.—Conditions found in Case 24; hyperalgesia found in a case of adhesive pericarditis. The maxima of the fourth, fifth and sixth dorsal areas were involved.

a clicking sound at the apex heard late in systole and hyperalgesia as shown in Figure 12, corresponding to the maxima of the fourth, fifth and sixth dorsal areas.

Adherent pericardium: 2 cases: These patients had neither pain nor hyperalgesia.

Thus in 83 cases of disease of the heart, pericardium and aorta, 33, or 39 per cent., had pain, and 6, or 7 per cent., had hyperalgesia. Of those complaining of pain, 18 per cent. showed hyperalgesia. The

inferior laryngeal, sternomastoid, sternonuchal and first, second, third, fourth, fifth, sixth, seventh, eighth, and ninth dorsal areas were found affected.

Carcinoma of esophagus: 3 cases; two of these patients had pain without hyperalgesia, the third complained only of discomfort in the epigastrium but had hyperalgesia. This patient, Case 60, gave a history, dating back six months, of discomfort in the epigastrium, followed by progressive difficulty in swallowing, loss of weight, and strength. Examination showed signs of an old right-side apical tuberculosis, an esophageal obstruction at the level of the heart, an enlarged liver and hyperalgesia as shown in Figure 13, corresponding to portions of the eighth and ninth dorsal areas. The patient later died and

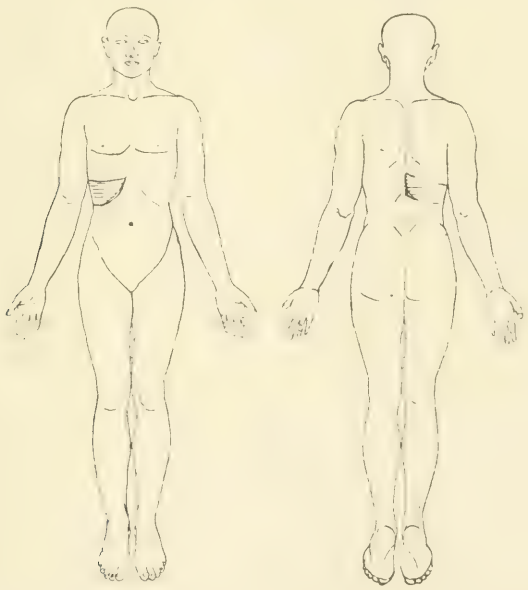


Fig. 13.—Conditions found in Case 60; hyperalgesia in a case of carcinoma of the esophagus. Portions of the eighth and ninth dorsal areas were involved.

necropsy showed healed tuberculosis on the right, carcinoma of the esophagus and gangrene of the left lung. In a case given by Head, the fifth, sixth, seventh and eighth dorsal areas were affected on both sides.

Hyperchlorhydria: 1 case; showed no pain or hyperalgesia.

Hypochlorhydria: 4 cases; showed no pain or hyperalgesia.

Ulcer of stomach: 9 cases; in each of these pain was a prominent feature. Hyperalgesia was found in three. Case 100 gave a history of attacks of sharp pain in the epigastrium and left back coming on about half an hour after meals relieved by vomiting and accompanied

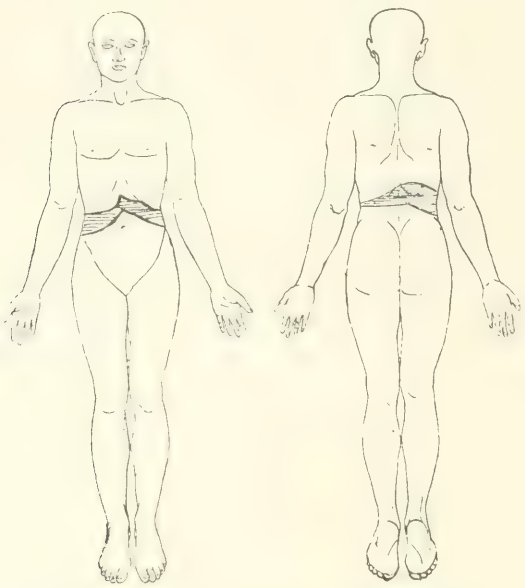


Fig. 14.—Conditions noted in Case 100; hyperalgesia found in a case of ulcer of the stomach. Portions of the eighth, ninth and tenth dorsal areas were involved.

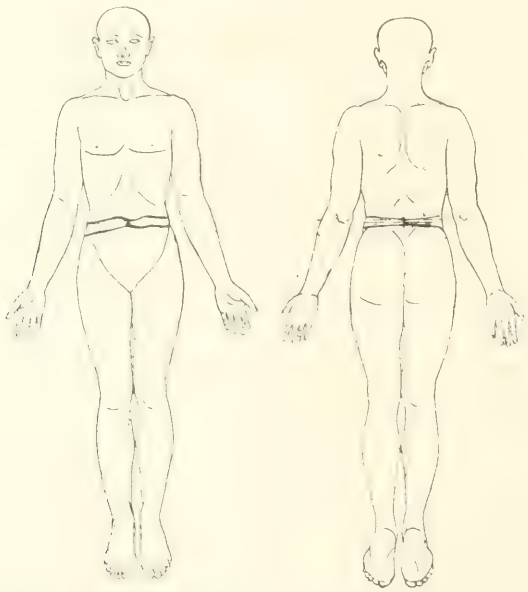


Fig. 15.—Conditions noted in Case 282; hyperalgesia found in a case of ulcer of the stomach. Portions of the ninth and tenth dorsal areas were involved.

by constipation, black stools and loss of weight. Blood had been frequently vomited. Examination showed marked tenderness under both costal margins and in the epigastrium, worse on the right side where pressure caused pain in the back, and hyperalgesia as shown in Figure 14, corresponding to portions of the eighth, ninth and tenth dorsal areas. Case 282 gave a history of pain in the right hypochondrium for six weeks coming on almost immediately after eating, lasting half an hour and accompanied by vomiting, loss of weight, dark colored stools, constipation and weakness. Examination showed tenderness in the right upper quadrant, occult blood in the stools, and hyperalgesia as shown in Figure 15, corresponding to portions of the ninth and

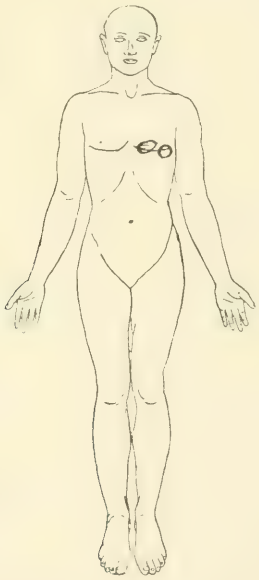


Fig. 16.—Conditions found in Case 372; hyperalgesia in a case of ulcer of the stomach. The maxima of the fifth and sixth dorsal areas were involved.

tenth dorsal areas. On subsequent admission to another hospital an hour-glass stomach was found at operation. The Wassermann reaction was positive in the blood. The patient in Case 372 had had symptoms at frequent intervals over a period of three years. Pain came on at any time, but particularly at night, was general over the abdomen or in the epigastrium, under the left costal margin or in the back, and was accompanied by nausea and by vomiting which usually gave relief. Examination showed tenderness and resistance in the epigastrium, anemia, and melena. Forty-five minutes after an Ewald meal the gastric contents showed free hydrochloric acid 34, total acid 74 and occult blood present. There was hyperalgesia as shown in Figure 16,

corresponding to the maxima of the fifth and sixth dorsal areas. Operation showed an ulcer of the greater curvature and a carcinoma of the lesser curvature. The segments involved here are much higher than those usually found affected by Head. (The record of the hyperalgesia in this case was unfortunately lost, but the areas shown and drawn from memory are reasonably accurate.)

Carcinoma of stomach: 11 cases; of these seven patients complained of pain; hyperalgesia was found in three cases. Case 372 was discussed above under ulcer of the stomach. Case 40 gave a history of loss of appetite, much pain in the lower abdomen coming on about four hours after meals, some nausea and belching, constipa-

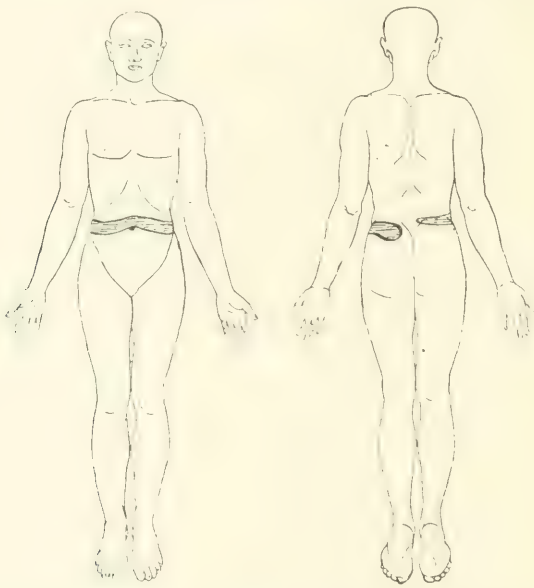


Fig. 17.—Conditions found in Case 40; hyperalgesia in a case of carcinoma of the stomach. Portions of the tenth and eleventh dorsal areas were involved.

tion and tarry stools, beginning eight or nine months before admission. Examination showed rigidity and tenderness in the upper abdomen, no free hydrochloric acid and a total acidity of only 4, no stasis or melena, and hyperalgesia as shown in Figure 17, corresponding to portions of the tenth and eleventh dorsal areas. At operation a hard nodular crescent-shaped carcinoma was found involving a large part of the stomach and attached to the head of the pancreas. The segments involved here are lower than those given by Head. Possibly this is accounted for by the involvement of the pancreas found at operation. The patient in Case 221 began to feel weak four months before admission, and lost his appetite. He grew constipated, had

sharp pain in the epigastrium radiating upward toward the sternum, vomited at various intervals after his meals, and lost 23 pounds weight. Examination showed a tender fixed mass the size of a hen's egg in the left hypochondrium, no free hydrochloric acid in the stomach contents after an Ewald meal, and hyperalgesia as shown in Figure 18, involving small portions of the ninth dorsal areas in the midline.

Tuberculosis of stomach: 1 case; this patient, Case 314, had had pain for fifteen months. Hyperalgesia was not found. The diagnosis made at operation was confirmed at necropsy. No other tuberculous lesions were found.

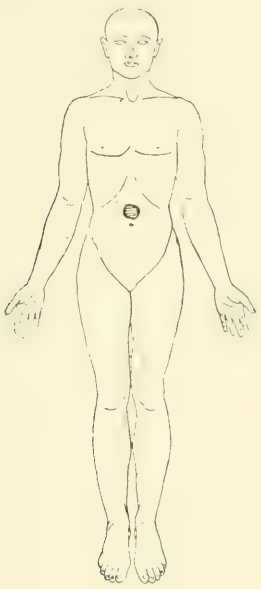


Figure 18

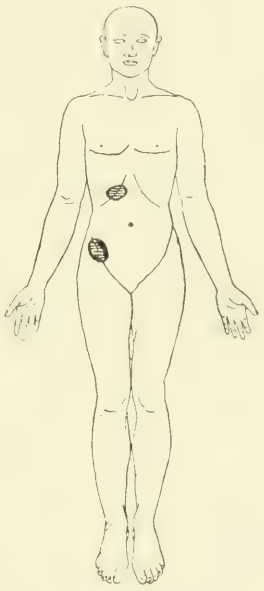


Figure 19

Fig. 18.—Conditions found in Case 221; hyperalgesia in a case of carcinoma of the stomach. Small portions of the ninth dorsal areas in the midline were involved.

Fig. 19.—Conditions noted in Case 222; hyperalgesia found in a case of ulcer of the duodenum. The maxima of the eighth and tenth dorsal areas were involved.

Ulcer of duodenum: 4 cases; all these patients complained of pain in the epigastrium. Hyperalgesia was found in Case 222. This patient gave a history of attacks of sharp pain under the right costal margin radiating at times all over the abdomen and to the spine, accompanied by nausea, and often relieved by food. Examination showed tenderness at McBurney's point, and slight resistance and tenderness in the region of the pylorus and on Murphy's maneuver. There was hyperalgesia as shown in Figure 19, corresponding approximately to

the maxima of the eighth and tenth dorsal areas. At operation an ulcer of the duodenum was found. The patient subsequently had attacks of pain in the right lower quadrant so that the involvement of the tenth dorsal area may have been due to a chronic appendicitis.

Thus in 25 cases of disease of the stomach, 16 patients, or 64 per cent., complained of pain and 6, or 24 per cent., had hyperalgesia. Of those who had pain 37 per cent. showed hyperalgesia. The fifth, sixth, eighth, ninth, tenth and eleventh dorsal areas were found involved.

Abscess of liver: 4 cases; three of these patients complained of pain; hyperalgesia was not found.

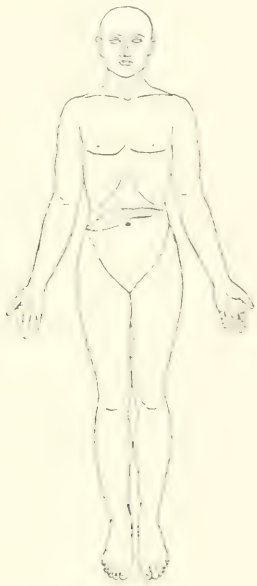


Fig. 20.—Conditions noted in Case 81; hyperalgesia found in a case of syphilis of the liver. Portions of the ninth and tenth dorsal areas were involved.

Syphilis of liver: 2 cases; one of these, Case 81, had had pain under the right costal margin and across the upper abdomen for one year with attacks of frequent bowel movements and passage of mucus and some blood. His skin had been darker for two years. Examination showed a small nodule on the surface of an otherwise normal liver, a palpable spleen, mucus in the stools without amebas, and hyperalgesia as shown in Figure 20, corresponding to portions of the ninth and tenth dorsal areas. The Wassermann reaction was positive in the blood and one injection of salvarsan relieved the pain completely.

Carcinoma of liver: 2 cases; both of these patients had pain. The patient in Case 369 had hyperalgesia. He gave a history dating back

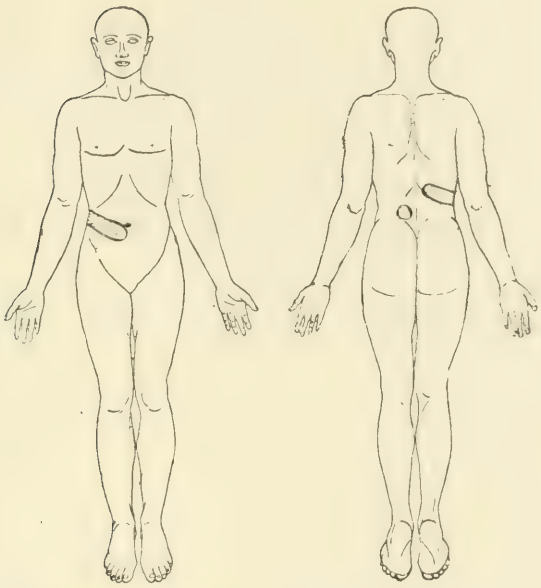


Fig. 21.—Conditions noted in Case 369; hyperalgesia found in a case of carcinoma of the liver. Portions of the tenth and the maximum of the eleventh dorsal areas were involved.

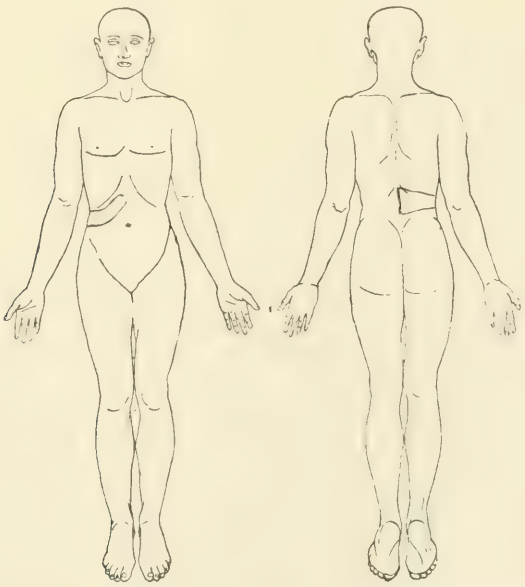


Fig. 22.—Conditions found in Case 138; hyperalgesia in a case of acute cholecystitis. Portions of the eighth, ninth and tenth dorsal areas were involved.

only ten days, of pain in the right shoulder blade, chest and abdomen, followed by cough, anorexia, and dark colored urine. On examination there was slight jaundice, a much enlarged liver and hyperalgesia as shown in Figure 21, corresponding to a portion of the tenth dorsal area and to the maximum of the eleventh. At operation the liver was found studded with tumor nodules. The involvement of the eleventh dorsal was unexplained unless by spreading or possible metastasis.

Cirrhosis of liver: 2 cases; neither of these patients had pain or hyperalgesia.

Cholecystitis, acute: 4 cases; two of these were in patients too ill to give any account of themselves. A third had severe pain without

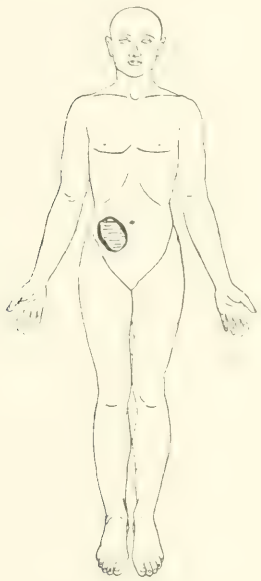


Figure 23

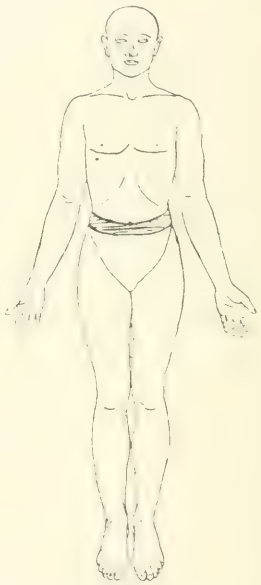


Figure 24

Fig. 23.—Conditions noted in Case 194; hyperalgesia in a case of cholelithiasis. Portions of the tenth and eleventh dorsal areas were involved.

Fig. 24.—Conditions found in Case 281; hyperalgesia found in a case of cholelithiasis. A portion of the tenth dorsal area was involved.

hyperalgesia. Case 138 was a typhoid patient who developed, during the course of his illness, pain under the right costal margin and hyperalgesia as shown in Figure 22, involving portions of the eighth, ninth and tenth dorsal areas. Nothing very definite could be determined about the gallbladder, but the pain and hyperalgesia were very suggestive of cholecystitis.

Cholecystitis, chronic: 1 case; this patient had pain at intervals; hyperalgesia was not found.

Cholelithiasis: 7 cases; four complained of pain and of these three had hyperalgesia. Case 194 gave a history of attacks of cramp-like abdominal pain accompanied by nausea, vomiting and sweating, followed by soreness of the abdomen and dating back for years. On examination he was found jaundiced, there were tenderness and rigidity in the region of the gallbladder and the urine contained bile. There was hyperalgesia as shown in Figure 23, rather indistinctly limited and corresponding to portions of the tenth and eleventh dorsal areas. At operation many gallstones were found. Here again a lower dorsal area than that given by Head was found. The patient in Case 281 had had several attacks characterized by intermittent griping pain in the epigastrium, slightly relieved by vomiting and accompanied by

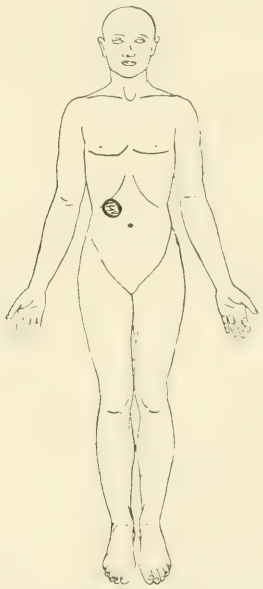


Fig. 25.—Conditions found in Case 438; hyperalgesia in a case of cholelithiasis. The maximum of the ninth dorsal area was involved.

pain in the right lower quadrant, weakness, nausea, and copious green stools. Examination showed obesity, considerable resistance and tenderness in the region of the gallbladder, slight tenderness at McBurney's point, a temperature of 101, and hyperalgesia as shown in Figure 24, corresponding to a portion of the tenth dorsal area. The patient in Case 438 was a woman of 61 who gave a history of attacks of cramp-like pain in the epigastrium coming on fifteen minutes after meals, radiating to the right and accompanied by nausea. Several months before admission she developed belching and distress after meals with a "numb" feeling in the right lower quadrant. There was

marked tenderness in the region of the gallbladder, less marked tenderness at McBurney's point, and pain on Murphy's maneuver. Forty-five minutes after an Ewald meal the stomach contents showed free hydrochloric acid 7, total acid 23. Hyperalgesia was found as shown in Figure 25, corresponding approximately with the maximum of the ninth dorsal area.

Hydrops of gallbladder: 1 case; this patient, Case 256, had no pain, but came for examination because of a mass on her right side which proved to be a much enlarged and slightly tender gallbladder. There was hyperalgesia as shown in Figure 26, corresponding to a point between the maxima of the twelfth dorsal and fourth sacral areas.

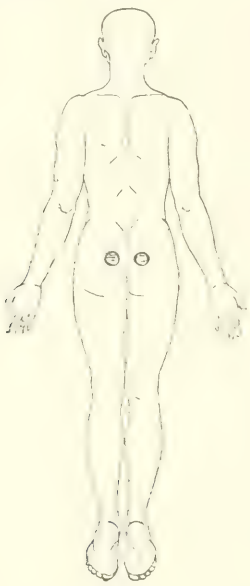


Fig. 26.—Conditions noted in Case 256; hyperalgesia found in a case of hydrops of the gallbladder. A point between the maxima of the twelfth dorsal and fourth sacral areas was involved.

Operation was refused and no other cause could be found for the hyperalgesia.

Carcinoma of gallbladder: 1 case; this patient had neither pain nor hyperalgesia.

Carcinoma of common duct: 1 case; no pain or hyperalgesia.

Catarrhal jaundice: 1 case; without pain or hyperalgesia.

Cholangitis, acute: 1 case; (necropsy finding in a case of carcinoma of the pancreas); pain and hyperalgesia were not noted.

Thus in 27 cases of disease of the liver and gall passages, twelve patients, or 44 per cent., had pain, and seven, or 25 per cent., showed

hyperalgesia. Of the patients who complained of pain, 58 per cent. had hyperalgesia. The areas involved were the eighth, ninth, tenth, eleventh (and twelfth?) dorsal areas.

Carcinoma of pancreas: 1 case; no pain or hyperalgesia.

Gastroenteritis, acute: 2 cases; this was a necropsy finding in one case. In the other it was due to mercuric chlorid poisoning from which the patient afterward died. There was abdominal pain without hyperalgesia.

Enteritis, acute: 1 case; no pain or hyperalgesia.

Enterocolitis, acute: 1 case; without pain or hyperalgesia.

Enteroptosis: 4 cases; two patients complained of pain which was attributed in one case to mucous colitis; hyperalgesia was not found.

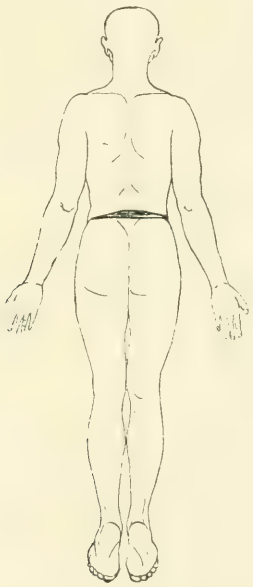


Fig. 27.—Conditions found in Case 156; hyperalgesia in a case of acute appendicitis. The posterior portion of the eleventh dorsal area was involved.

Intestinal neurosis: 1 case; without pain or hyperalgesia.

Tuberculosis of intestines: 2 cases; one of these patients was in a stupor when admitted and made no complaint. One had vague left-side abdominal pain without hyperalgesia. The lesions were demonstrated at necropsy in both cases.

Appendicitis, acute: 6 cases; pain was pronounced in each of these; hyperalgesia was found in one. This patient, Case 156, gave a history of severe general abdominal pain for three days, with constipation, chills, fever, sweats, and aching pain in the head and back. Examination showed at first only slight tenderness at McBurney's point, later a

small mass and hyperalgesia as shown in Figure 27, corresponding with the posterior portion of the eleventh dorsal area. At operation an abscess was found about the appendix.

Appendicitis, chronic: 11 cases; one of these patients, Case 438, already discussed under cholelithiasis, complained of "numbness" in the right lower quadrant where tenderness was found at McBurney's point. Nine patients complained of pain, which was, in five cases, in the right lower quadrant; in four cases, in the epigastrium. Hyperalgesia was found in three cases. Case 155 gave the unusual history of pain under the sternum on swallowing, inability to eat solid food, and constant distress in the upper abdomen. There was some tender-

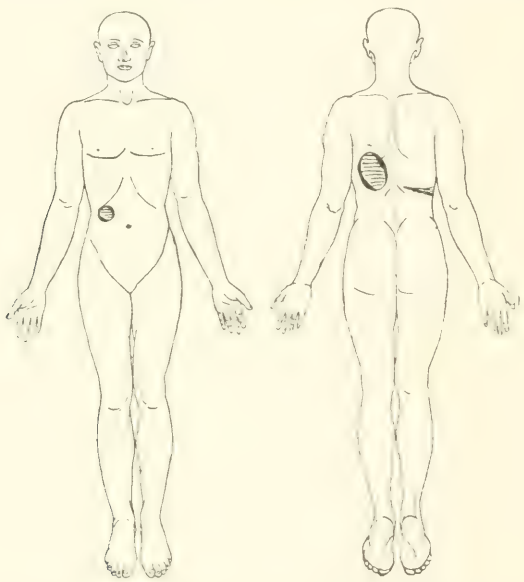


Fig. 28.—Conditions noted in Case 155; hyperalgesia found in a case of chronic appendicitis. The maximum anteriorly and a portion posteriorly of the ninth dorsal area were involved.

ness in the region of the gallbladder and hyperalgesia as shown in Figure 28, corresponding with the maximum anteriorly and a portion posteriorly of the ninth dorsal area on the right. Portions of the sixth, seventh, eighth and ninth dorsal areas posteriorly on the left were also involved. It was thought that a chronic cholecystitis might be the cause of the pain. On opening the abdomen, the gallbladder was found normal but the appendix was chronically inflamed. Its removal relieved the patient of all his symptoms. Although the ninth dorsal area receives sensory fibers from the intestine, reference of the pain and hyperalgesia to a point so far removed as the sixth dorsal area

seems difficult to explain except by "spreading." The patient in Case 165 had had pain in the right lower quadrant at intervals for three years, accompanied by fever and chills and usually by belching. Examination showed marked tenderness over the appendix and hyperalgesia as shown in Figure 29, corresponding rather closely with the tenth dorsal area. The third patient, Case 166, gave a history of distress after eating, belching, anorexia, nausea, and finally of griping pain and burning in the epigastrium, worse after meals. There was tenderness and resistance at McBurney's point and indefinite hyperalgesia as shown in Figure 30, corresponding to a portion of the tenth dorsal area.

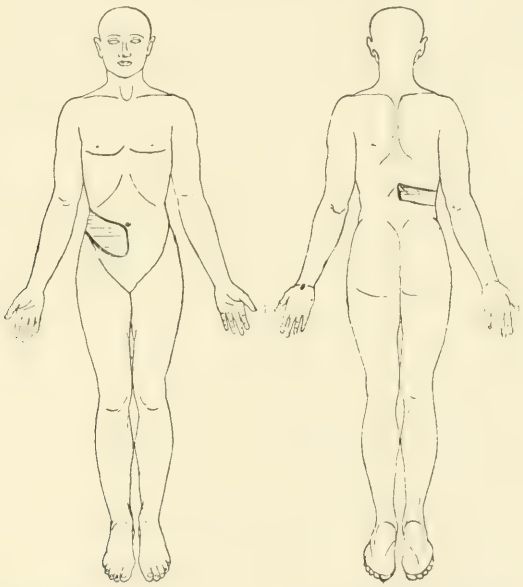


Fig. 29.—Conditions noted in Case 165; hyperalgesia found in a case of chronic appendicitis. The area involved corresponded rather closely with the tenth dorsal.

Tuberculosis of appendix: 1 case; Case 252: this patient was a young student who, as long as he could remember, had had dull pain in the lower abdomen especially aggravated by defecation. At times there had been sharp pain in the right lower quadrant. On examination tenderness was found in the region of the appendix and over the sigmoid. There was hyperalgesia as shown in Figure 31, corresponding to the maxima of the twelfth dorsal areas. Operation some months later showed tuberculosis of the appendix.

Tuberculosis of cecum: 1 case; this patient was uremic on admission and the lesion was found only at necropsy. There was a history of pain in the epigastrium.

Colitis, acute: 5 cases; this was found in each instance only at necropsy. One patient had had colicky pain in the abdomen for a month but frequent stools only for five days before admission. There was no hyperalgesia.

Colitis, chronic: 7 cases; two of these patients complained of pain in the epigastrium; hyperalgesia was not found.

Constipation: This was associated with large amounts of mucus in the stools in two cases, one patient having pain in the epigastrium. In seven cases it was the main or only diagnosis. Three of these latter patients complained of pain but did not show hyperalgesia. In Case 7, hyperalgesia was found without complaint of pain. The history was of fulness after eating, palpitation, headache, and a film over the eyes. Hyperalgesia was found as shown in Figure 32, corresponding approximately to the maxima of the tenth and of the sixth dorsal areas. Examination was otherwise negative and daily bowel movements gave him complete relief.

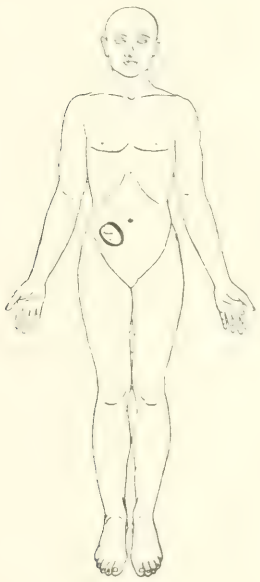


Figure 30

Fig. 30.—Conditions noted in Case 166; hyperalgesia found in a case of chronic appendicitis. A portion of the tenth dorsal area was involved.

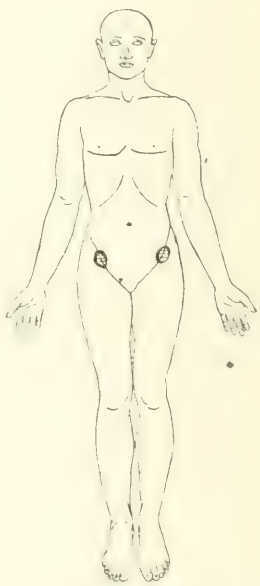


Figure 31

Fig. 31.—Conditions noted in Case 252; hyperalgesia found in a case of tuberculosis of the appendix. The maxima of the twelfth dorsal area were involved.

Dysentery, entamebic: 3 cases; two of these patients complained of pain; hyperalgesia was not found.

Thus in fifty-one cases of disease of the small and large intestines, twenty-seven, or 52 per cent., had pain, and six, or 11 per cent., had hyperalgesia. Of the patients who complained of pain, 22 per cent. showed hyperalgesia. The (sixth, seventh, eighth?), ninth, tenth, eleventh and twelfth dorsal areas were involved.

Peritonitis, acute, general: 3 cases; this was terminal in two patients who were too ill to give any account of themselves. In a third there was right-side abdominal pain without hyperalgesia.

Tuberculosis of peritoneum: 2 cases; both of these patients had pain in the upper abdomen without hyperalgesia.

Peritonitis, pelvic: 1 case; no pain or hyperalgesia.

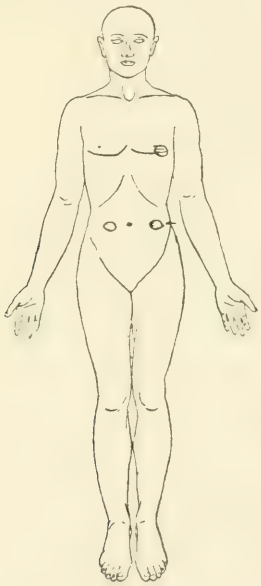


Fig. 32.—Conditions noted in Case 7; hyperalgesia found in a case of constipation. The maxima of the tenth and sixth dorsal areas were involved.

Prostatitis, acute: 1 case; this patient had pain on urination but no hyperalgesia over the sacral areas (discussed under pyelitis).

Prostatitis, chronic: 2 cases; without pain or hyperalgesia.

Pyelitis: 2 cases; this was a necropsy finding in one patient who entered in uremia and was found to have an ascending nephritis. Case 265 gave a history of slight pain in the left lower back for several days one year before. Four days before admission this pain returned with chilly sensations, fever, anorexia, frequent and painful urination and a urethral discharge. On examination there was some muscular spasm on the left side of the abdomen, pain on bimanual palpation of the left kidney, tenderness in the left costovertebral angle and

moderate elevation of temperature to 101. The prostate was found enlarged and its secretion purulent. Pus was found in the urine from both ureters. Roentgenologic examination was negative for stone. Phenolsulphonephthalein appeared from the right ureter in three minutes, but on the left it had not appeared in forty minutes. Guinea-pigs were injected but were not found tuberculous. There was hyperalgesia as shown in Figure 33, involving portions of the tenth, eleventh and twelfth dorsal areas. As will be seen in other records this hyperalgesia was found rather characteristic for disease of the kidney and ureter.

Tuberculosis of kidney: 1 case; this patient had had pain in the right lower quadrant; there was no hyperalgesia.

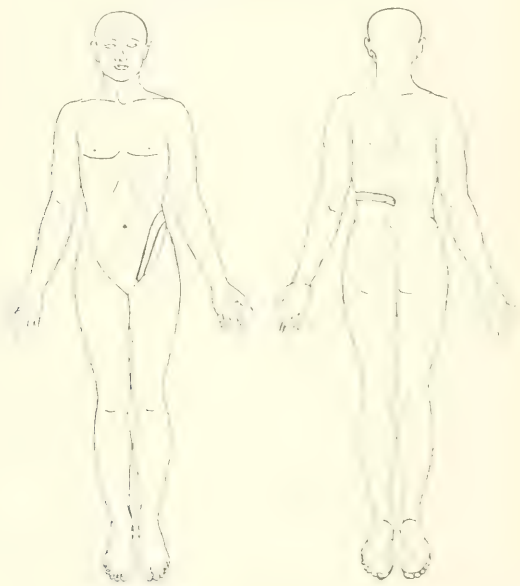


Fig. 33.—Conditions found in Case 265; hyperalgesia found in a case of pyelitis. Portions of the tenth, eleventh and twelfth dorsal areas were involved.

Nephrolithiasis: 5 cases; all these patients had pain; three had hyperalgesia. The patient in Case 247 had had three attacks of severe sharp pain on the left side in the region of the tip of the twelfth rib, accompanied by sweating, vomiting and anuria and followed by the passage of normal urine in twenty-four hours. The last attack came four days before admission. Examination showed tenderness in the region of both kidneys but especially marked on the left, and hyperalgesia as shown in Figure 34, corresponding approximately to the lateral maximum of the tenth dorsal area. The urine contained pus, and staphylococci were found in smears and grown in pure culture

from a catheterized specimen. The bladder wall was slightly inflamed. A ureteral catheter entered the left ureter 15 cm. but no farther, and cargentos could not be injected beyond this point. Roentgenologic examination showed a shadow 1 cm. in diameter at the tip of the transverse process of the third lumbar vertebra on the left side. The patient in Case 251 had had slight tenderness in the left side of the abdomen for two years. One week before admission he developed pain in the left flank radiating into the scrotum, with tenderness in the left lumbar region. There was considerable tenderness extending from the left costovertebral angle to the left lower quadrant, slight elevation of temperature to 99.2, many red blood cells in the urine and hyperalgesia as shown in Figure 35, involving portions of the tenth,

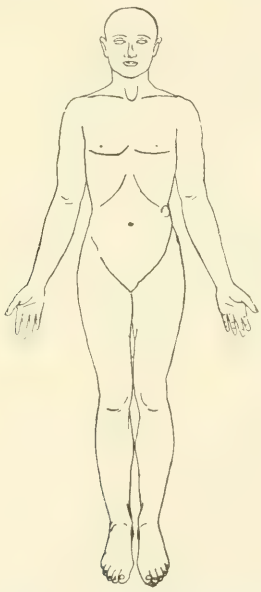


Fig. 34.—Conditions found in Case 247; hyperalgesia found in a case of nephrolithiasis. The maximum of the tenth dorsal area was involved.

eleventh and twelfth dorsal areas. Cystoscopy showed a small stone projecting from the end of the ureter. The patient in Case 389 gave a history of pain in the back following a gonorrheal urethritis fourteen years before. Two days before admission he had pain in the right lower quadrant with nausea, fever, chills and soreness of the abdomen. There was also complaint of headache, spots before the eyes, and dyspnea on exertion. Examination showed a heavy cloud of albumin, a large number of granular casts and a few white blood cells in the urine, but was otherwise negative. Two weeks after admission there was severe pain in the left flank and testicle and hyperalgesia as shown

in Figure 36, corresponding approximately with the lateral maximum of the tenth dorsal area. The Roentgen ray showed probable stone in the right kidney. Cystoscopy and ureteral catheterization gave negative results and a culture of the urine remained sterile. The patient in Case 300 had had dull aching pain in the left flank for three years and soreness just below the umbilicus somewhat relieved by defecation. Both these conditions had been much relieved by a tight binder. For six months before admission she had had every few weeks attacks of sudden distress in the epigastrium after food but was not relieved by the vomiting which followed. The patient was of the type of congenital asthenia described by Stiller. The tonsils were

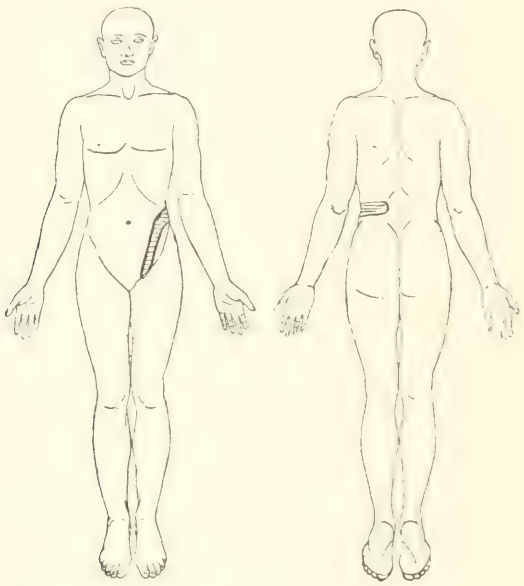


Fig. 35.—Conditions noted in Case 251; hyperalgesia found in a case of nephrolithiasis. Portions of the tenth, eleventh and twelfth dorsal areas were involved.

enlarged, there were some changes at the right apex, both kidneys were movable to the third degree, and there was general abdominal tenderness especially marked in the left flank, over the colon and above the pubes. Hyperalgesia was found as shown in Figure 37, corresponding to that previously described (tenth, eleventh, twelfth dorsal) and including, in addition, portions of the seventh, eighth and ninth dorsal areas posteriorly. These latter were not found by Head to be involved in disease of the kidney. Further investigation to determine the cause of this pain and hyperalgesia were unfortunately not carried

out because following tonsillectomy, a forced diet and a proper abdominal belt there was a gain in weight and no further complaint.

Nephroptosis: 3 cases; none of these patients had pain which could be attributed to this condition, with the possible exception of the patient in Case 300 just discussed.

Thus in 11 cases of disease of the kidney and ureters, 7, or 63 per cent., had pain and 5, or 45 per cent., showed hyperalgesia. Of those patients who had pain, 71 per cent. had hyperalgesia.

Cystitis, acute: 1 case; this patient had pain without hyperalgesia.

Cystitis, subacute: 1 case; without pain or hyperalgesia.

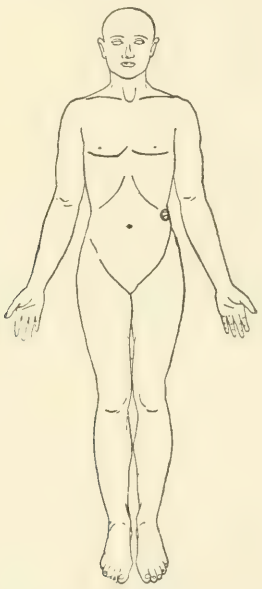


Fig. 36.—Conditions noted in Case 389; hyperalgesia found in a case of probable nephrolithiasis. The maximum of the tenth dorsal area was involved.

Cystitis, chronic: 2 cases; without pain or hyperalgesia referable to bladder. One of these cases, Case 247, was discussed under nephrolithiasis.

Salpingitis, acute: 1 case; there was marked pain here without hyperalgesia.

Arthritis deformans of spine: 7 cases; these cases were grouped together because in several of them pain was attributed by the patient to visceral disease. In this group, six patients complained of pain, which was abdominal in two cases, in the back in three cases and in the hip and leg in one case. There was hyperalgesia in three of these cases. Case 98 gave a history of pain in the left buttock, thigh and leg occurring only on motion of the leg. On examination there was

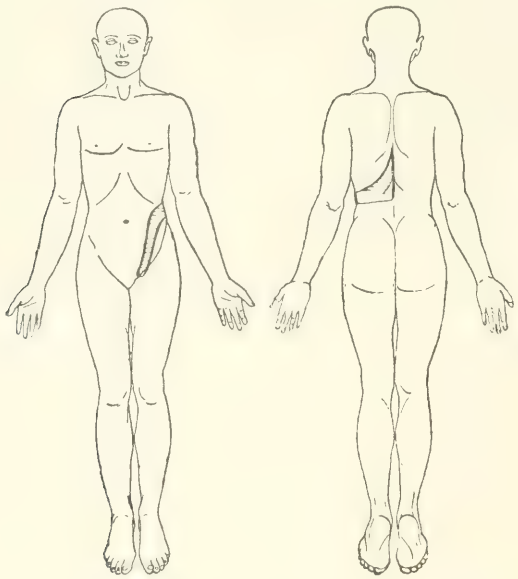


Fig. 37.—Conditions noted in Case 300; hyperalgesia found in a case of possible nephrolithiasis. Portions of the seventh, eighth, ninth, tenth, eleventh and twelfth dorsal areas were involved.

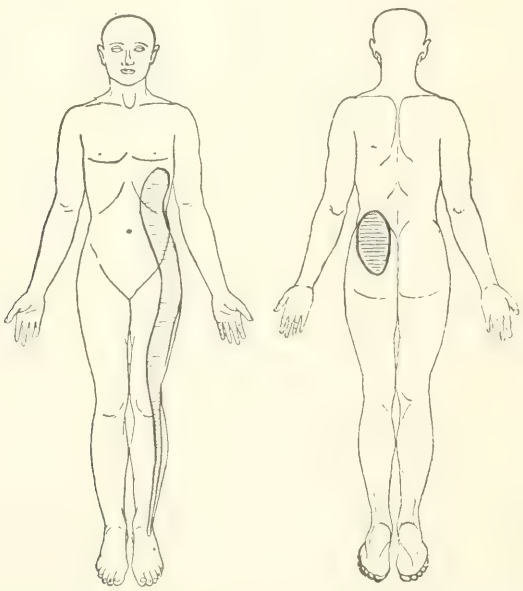


Fig. 38.—Conditions noted in Case 98; hyperalgesia found in a case of arthritis deformans of the spine. Portions of the dorsal areas from the sixth to the twelfth and of the second, third, fourth and fifth lumbar areas were involved.

tenderness to pressure over the lower lumbar vertebrae and upper sacrum, some pain on hyperextension of the lumbar spine, and all movements of the spine were slightly limited. Roentgenographic examination showed osteoarthritis of the lumbar spine, lateral displacement to the left of the fourth and fifth lumbar vertebrae and apparent bony union of the two vertebrae on the left side. There was hyperalgesia as shown in Figure 38, involving portions of the dorsal areas from the sixth to the twelfth passing through the second, third and fourth lumbar areas, to which visceral pain is not referred, and terminating in the fifth lumbar area. Posteriorly the hyperalgesia

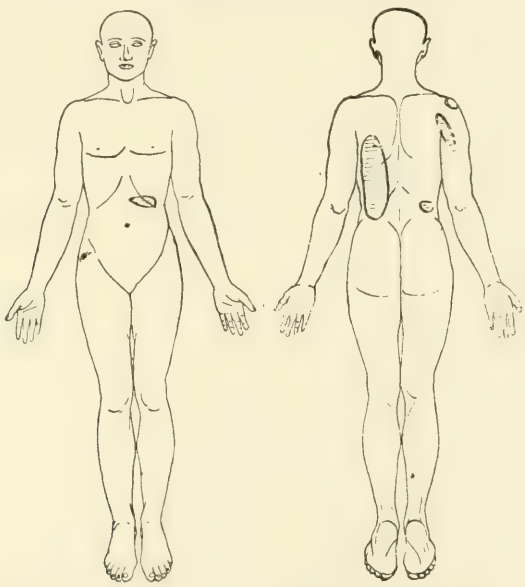


Fig. 39.—Conditions noted in Case 83; hyperalgesia found in a case of syphilitic infection of long standing. Portions of the sixth, seventh, eighth, ninth and tenth, and the maximum of the eleventh dorsal areas were involved. No special organ could be accused.

involved principally the eleventh and twelfth dorsal areas. Careful examination failed to reveal any visceral disease to which this hyperalgesia could have been attributed. This case may serve as a type of the other cases showing hyperalgesia as a result of vertebral disease.

Syphilis: Of 54 cases of syphilitic infection only six patients had pain which could not be traced to one of the viscera. Three of these patients showed hyperalgesia. Case 83 gave a history of sudden diplopia a week before, followed in twelve hours by sharp pain in the left shoulder radiating to the chest and right shoulder, with some headache, vomiting and loss in weight. There was a paralysis of the right superior oblique, some chronic lung changes, muscular resistance on

the right side of the abdomen, absence of Achilles reflexes and hyperalgesia as shown in Figure 39, corresponding anteriorly to a portion of the eighth, posteriorly on the left to portions of the sixth, seventh, eighth, ninth and tenth and on the right approximately to the maximum of the eleventh dorsal areas. Two small hyperalgesic areas occur in the areas to which visceral pain is not referred. The spinal fluid contained 30 cells per cubic millimeter, increased globulin and albumin, but the Wassermann reaction was negative both in the blood and in the spinal fluid. He was much relieved by an injection of salvarsan. This case is perhaps an instance of so-called "spreading," the cause of the original disturbance being possibly an alcoholic gastritis. The

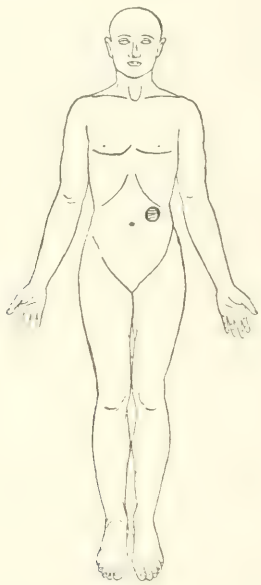


Fig. 40.—Conditions noted in Case 404; hyperalgesia found in a case of syphilitic infection. The maximum of the ninth dorsal area was involved. Probably the stomach was the cause of the referred pain.

patient in Case 404 had had sharp burning pain in the left upper quadrant after meals for five years, with belching, constipation, pain in head and shoulders and loss of weight. A gastro-enterostomy had given him some relief, but his symptoms returned. On admission there were two laparotomy scars above the umbilicus and hyperalgesia as shown in Figure 40, corresponding approximately to the maximum of the ninth dorsal area. The Wassermann reaction was positive and one injection of salvarsan relieved all his symptoms. The patient in Case 71 had had severe knife-like pain under the left costal margin coming on a week previously with "unconsciousness"? and lasting

almost an hour. A year before he had had a similar attack. On admission he still had severe pain in the same situation. There was a pigmented line on the gums about the incisors (probably racial), considerable arterial thickening, a palpable spleen, no stippling of the red blood cells and a positive Wassermann reaction in the blood. Abdominal massage brought on severe pain which was almost immediately controlled with atropin. There was hyperalgesia as shown in Figure 41. One injection of salvarsan gave him much relief.

Functional diseases: There were twelve patients in whom a sufficient cause could not be found to explain the symptoms. Of these, five complained of pain, one showing hyperalgesia. This patient, Case 274,

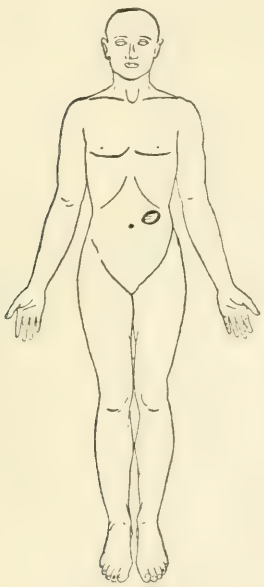


Figure 41

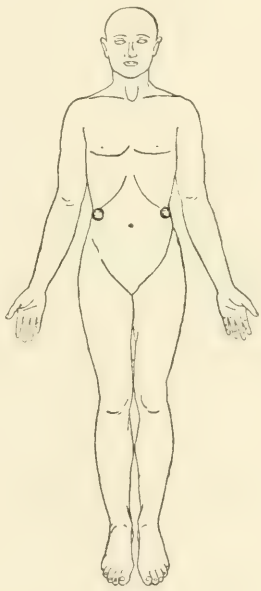


Figure 42

Fig. 41.—Conditions noted in Case 71; hyperalgesia found in a case of abdominal syphilis. The maximum of the ninth dorsal area was involved.

Fig. 42.—Conditions noted in Case 274; hyperalgesia found in a case of functional disease. The maxima of the tenth dorsal area were involved.

gave a history of lumbar pain, pain in the limbs, weakness, palpitation, vomiting, nervousness and dizziness. He felt oppressed in heated rooms and in the presence of other people. Examination was negative except for hyperalgesia as shown in Figure 42, involving the maxima of the tenth dorsal areas. One patient in this group, Case 59, had hyperalgesia without pain. He was a man of 40 who complained of attacks of palpitation dyspnea, headache and frequent urination which he had had from the age of 13. Except for some asymmetry of the

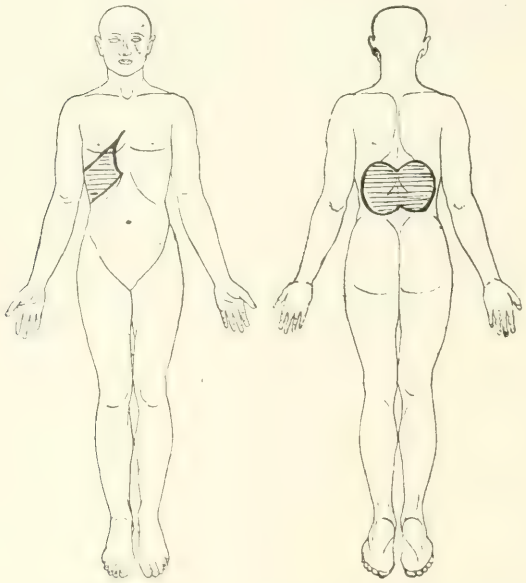


Fig. 43.—Conditions noted in Case 59; hyperalgesia found in a case of functional disease. Portions of the sixth, seventh, eighth, ninth and tenth dorsal areas were involved.

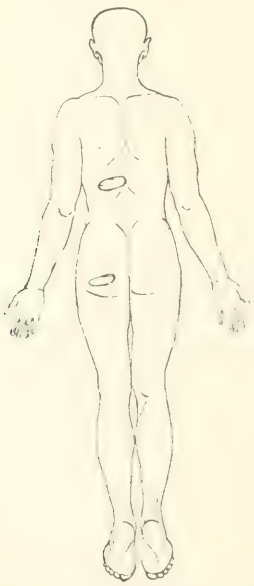


Fig. 44.—Conditions noted in Case 244; hyperalgesia corresponding to portions of the eighth, ninth and tenth dorsal and second sacral areas could not be explained.

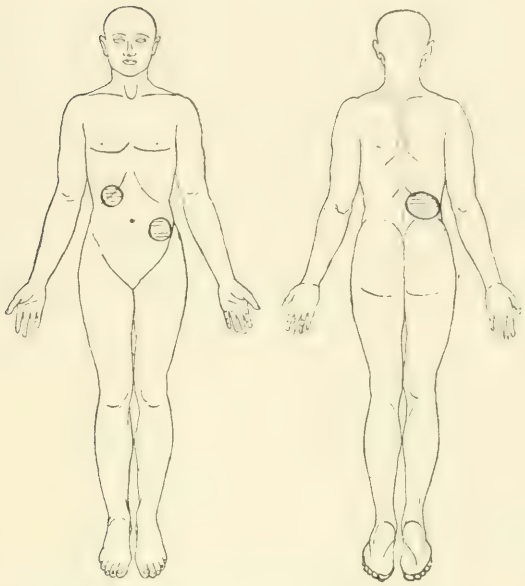


Fig. 45.—Conditions noted in Case 127; hyperalgesia corresponding to the maximum of the ninth, and portions of the tenth and eleventh dorsal areas could not be explained.

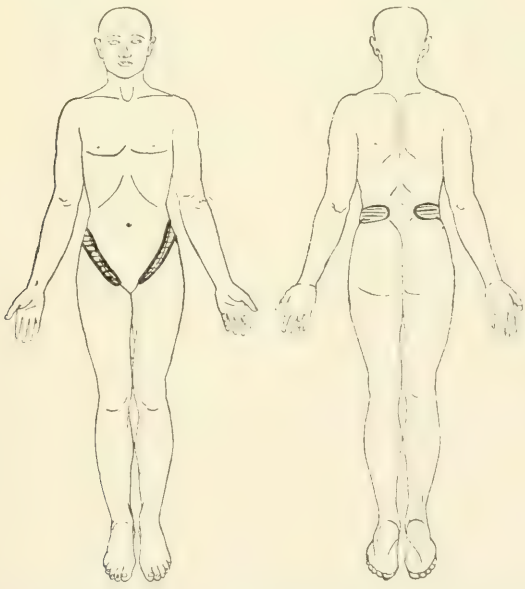


Fig. 46.—Conditions noted in Case 406; hyperalgesia corresponding to the eleventh dorsal areas on both sides could not be explained.

chest, examination was negative. There was hyperalgesia as shown in Figure 43, involving portions of the sixth, seventh, eighth, ninth and tenth dorsal areas. He was much relieved by a cantharides blister on his spine.

Typhoid Fever: 6 cases; four of these patients had pain; hyperalgesia was found in one case, Case 138, discussed under cholecystitis.

Unexplained: 4 cases. Case 244 gave a history of painful swelling of the great toe with some pain in the hip, sweating, lassitude, and loss in weight. On examination there were tophi in the ears, a few wheezy râles over the right upper chest, fibrillating auricles, some redness and swelling of the great toe on the right, crepitations of the knee joints

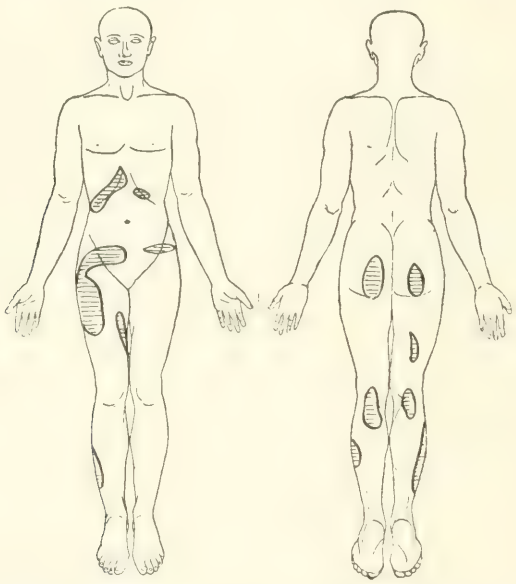


Fig. 47.—Conditions noted in Case 107; hyperalgesia corresponding to portions of the seventh, eighth, ninth, eleventh and twelfth dorsal, first lumbar, and second, third and fifth sacral areas could not be explained.

and hyperalgesia as shown in Figure 44, corresponding to portions of the eighth and ninth dorsal and a portion of the second sacral areas. The patient in Case 127 had had shortness of breath and a sense of pressure under the sternum for two months, and transient blurring of vision for three years. On examination there was Cheyne-Stokes breathing, a coated tongue, rather marked arterial thickening, a blood pressure of 200 mm. Hg, a few râles at the right base and tenderness to the left of the umbilicus and in the costovertebral angles. The urine contained much albumin, many casts and a few white blood cells. There was nephritic edema of the fundi oculi. Hyperalgesia was

found as shown in Figure 45, corresponding to the maximum of the ninth, and portions of the tenth and eleventh dorsal areas. A roentgenogram of the kidney was negative for stone and the hyperalgesia remained unexplained. Case 406 gave a history beginning four months before of dizziness and weakness coming on in attacks, attributed to eating meat or potatoes, or drinking milk, and accompanied by nausea and gradually by some loss in weight. There was very slightly diminished hearing on the right and slight generalized abdominal tenderness on physical examination. Ear tests showed the caloric absent on the right and spontaneous rotary nystagmus to the right. On turning to the right there was nystagmus for fifteen seconds rotatory to the right; on turning to the left there was nystagmus for thirty seconds rotatory to the right. The cochlea was intact on both sides. The diagnosis was neuritis of the vestibular branch of the eighth cranial nerve. There was hyperalgesia as shown in Figure 46, corresponding approximately to the eleventh dorsal area on both sides, for which careful examination failed to reveal any cause. The patient in Case 107 had had belching, sour eructations, heaviness in the epigastrium, rumbling in the head, dizziness and weakness following a blow on the head three months before admission. Examination showed slight deafness on the left, some muscular resistance in the epigastrium and pronated feet. The hemoglobin was 68 per cent. Roentgenologic examination showed possible adhesions about the pylorus. Hyperalgesia was found as shown in Figure 47, involving portions of the seventh, eighth, ninth, eleventh and twelfth dorsal, first lumbar, second, third and fifth sacral areas. No cause was found for this extensive involvement.

CONCLUSIONS

In this series of 460 hospital cases, hyperalgesia was a frequent finding in visceral disease.

In diseases of the lungs hyperalgesia was found in 3 per cent. of the cases, or in 13 per cent. of those who complained of pain.

In diseases of the heart and aorta, hyperalgesia was found in 7 per cent. of the cases, or in 18 per cent. of those who complained of pain.

In diseases of the stomach, hyperalgesia was found in 24 per cent. of the cases, or in 37 per cent. of those who complained of pain.

In diseases of the liver and gall passages, hyperalgesia was found in 25 per cent. of the cases, or in 58 per cent. of those who had pain.

In diseases of the intestines hyperalgesia was found in 10 per cent. of the cases or in 22 per cent. of those who had pain.

In diseases of the kidney and ureters hyperalgesia was found in 45 per cent. of the cases, or in 71 per cent. of those who complained of pain.

Whole dorsal areas as outlined by Head were rarely found, but certain maxima were frequently found.

The large number of areas over which hyperalgesia may be found in disease of each viscus, and the number of viscera supplied by each segment, made hyperalgesia of practically no importance in diagnosis with the possible exception of diseases of the kidney in which it had a somewhat characteristic form.*

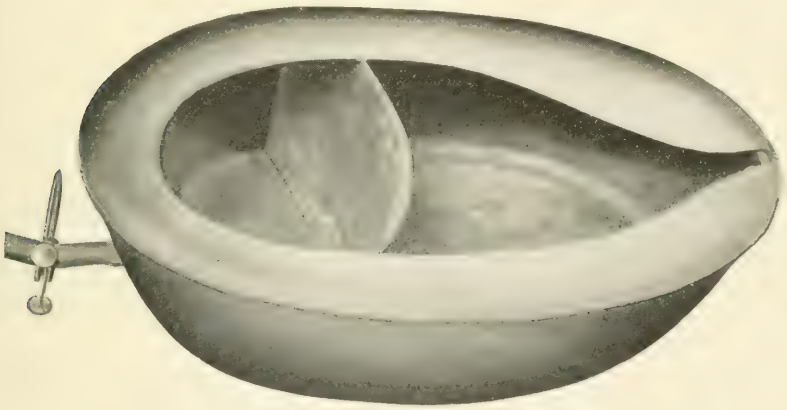
240 Stockton Street.

* This investigation was carried on in the medical wards of Lane Hospital, Leland Stanford Jr. University Medical School. Permission to report the cases is due to the kindness of Dr. R. L. Wilbur, dean.

AN APPARATUS FOR THE QUANTITATIVE COLLECTION OF URINE FROM WOMEN

OTTO FOLIN, M.D., AND W. DENIS, PH.D.
BOSTON

The difficulty, in fact, we may almost say the practical impossibility, of obtaining accurate twenty-four-hour quantities of urine from female hospital patients has probably been recognized by every investigator who has attempted to conduct metabolism experiments on this class of subjects. Our own experience has been that even when under the constant supervision of competent nurses, intelligent female patients (particularly when under the influence of cathartics) will frequently lose from 5 to 25 per cent. of the daily amount of urine.



Apparatus for quantitative collection of urine from women.

In order to overcome this difficulty we have devised a "divided pan," an illustration of which is shown. This pan, which is made of sheet copper, nickel plated, is constructed along the lines of the ordinary hospital bed pan, being 14 inches long by 9¾ inches wide; the front end is 4¼ inches high, the back 9½ inches; 6¼ inches from the front end is a curved slanting partition which divides the vessel into two chambers, one for the reception of urine, the other for feces. The front or urine compartment is provided with an outlet consisting of a short piece of copper tubing half an inch in diameter and closed by means of a piece of rubber tubing and a pinchcock. The top of the pan is so constructed that it may be easily removed for cleaning.

We have now had this apparatus in use for many months in the women's and children's wards of the Massachusetts General Hospital, during which time it has been used by a large number of patients with practically invariable success. It may be used in bed with the subject in the recumbent position, or in the case of patients well enough to be up and about the ward, may be placed on a low stool.

While the device was introduced primarily for our metabolism experiments, it has been found useful in many cases in the routine collection of urine or feces, particularly in the case of very stupid patients and those unable to speak English.

Harvard Medical School.

THE BACTERIAL FLORA OF LYMPHATIC GLANDS*

ARTHUR L. BLOOMFIELD, M.D.
BALTIMORE

That the regional lymphatic glands can filter out bacteria from an infected area has been conclusively shown with reference to numerous organisms by simultaneously cultivating them from both situations. More generalized invasion of glands in agonal and postagonal states is also a matter of common experience, many special studies having been made on this point, among which may be mentioned the recent ones of Southard and Canavan.[1] In certain specific diseases, furthermore, the causal organisms may be present in the glands in association with the characteristic changes—notably in tuberculosis. Within the last two years, a great deal of interest has arisen in the latter type of gland infection, stimulated especially by bacteriologic studies of Hodgkin's disease, and other conditions associated with glandular enlargements of obscure origin.

Bunting and Yates,[2] in 1913, almost simultaneously with Negri and Mieremet,[3] isolated in pure culture by aerobic methods, from the lymph nodes of patients in three cases of Hodgkin's disease, a pleomorphic diphtheroid bacillus. In two other cases, the organism was recognized, but not secured in pure culture. Bunting and Yates felt that they were probably dealing with the same organism described by Negri and Mieremet in two cases,[3] and possibly with the bodies demonstrated morphologically by Fraenkel and Much,[4] in 1910. In spite of the frequent association of other organisms, especially staphylococci, in the cultures, they felt that the diphtheroid bacillus was the one which most probably bore some specific relation to the disease, and were encouraged in this view by the development in a monkey, after injection of cultures, of a chronic progressive lymphadenitis, bearing some resemblance to Hodgkin's disease,[5] and finally,[6] by the production of progressive general glandular enlargement, with fever and leukocyto-

* Submitted for publication May 4, 1915.

* From the Medical Clinic of the Johns Hopkins Hospital.

1. Southard, E. E., and Canavan, M. M.: Jour. Med. Research, 1915, xxxi, 339.
2. Bunting, C. H., and Yates, J. L.: The Archives Int. Med., 1913, xii, 236.
3. Negri, E., and Mieremet, C. W. G.: Centralbl. f. Bacteriol., 1913, lxviii, 292 (original).
4. Fraenkel, E., and Much, H.: Ztschr. f. Hyg., 1910, lxvii, 159.
5. Bunting, C. H., and Yates, J. L.: Jour. Am. Med. Assn., 1913, lxi, 1803.
6. Bunting, C. H., and Yates, J. L.: Jour. Am. Med. Assn., 1914, lxii, 516.

sis, leading to the death of the animal. From the lesions, the diphtheroid organism was recovered in pure culture.

Billings and Rosenow[7] were also successful in cultivating from Hodgkin's nodes diphtheroid bacilli similar to those described by the previous workers, and confirmed the frequent association of staphylococci with this organism. They reported favorable results from treatment with vaccines. Rosenow later[8] published extensive cultural studies on tissues of various sorts. He isolated from the lymph nodes in acute and chronic arthritis, erythema nodosum, and Hodgkin's disease, a great many organisms, notably, streptococci, diphtheroid bacilli, *B. welchii,* and others. He noted, however, that none of these organisms was strictly limited to any one condition, and that often two or more were obtained from the same source. He was somewhat in doubt as to the interpretation of these findings, but inclined toward the position that in most cases the organisms were related causally to definite diseases.

Several less extensive studies have recently appeared, among which may be mentioned that of Lanford,[9] who recovered diphtheroid organisms from the nodes in several cases of Hodgkin's disease, tuberculosis and lymphosarcoma; of Steele,[10] who reports similar findings in a case of lymphatic leukemia; and, finally, the note by Rhea and Falconer,[11] on the cultivation of a pleomorphic diphtheroid bacillus from the nodes in a case of Hodgkin's disease.

The general result of these studies seemed to be the proof that viable bacteria are frequently present in lymph nodes *intra vitam* in conditions other than acute inflammation. The significance of the organisms, however, was by no means established. Thus, several possibilities immediately arose: (1) The glands might be filtering out saprophytic organisms which had accidentally become introduced into the body; (2) there might be a normal saprophytic flora of glands analogous to that of the skin; (3) the organisms might have persisted in the glands in more or less attenuated form after a previous acute invasion; (4) changes in the gland might have predisposed to invasion by certain organisms; and (5), specific organisms might be associated with specific histologic changes.

The following cultural studies were made, rather in the attempt to classify the bacteria obtained from glands, according to the above schema, than to investigate any particular diseases with the hope of finding an etiologic agent.

7. Billings, F., and Rosenow, E. C.: Jour. Am. Med. Assn., 1913, lxi, 2122.
8. Rosenow, E. C.: Jour. Am. Med. Assn, 1914, lxiii, 903.
9. Lanford, J. A.: Am. Jour. of Trop. Dis. and Prev. Med., 1914, ii, 191.
10. Steele, A. E.: Boston Med. and Surg. Jour., 1914, clxx, 123.
11. Rhea, J., and Falconer, E. H.: The Archives Int. Med., 1915, xv, 438.

MATERIAL

It seemed advisable to draw material from as wide a range of conditions as possible. The glands which have been studied may be divided into two general groups. The first has been designated as the "normal" group, although it is recognized that no lymphatic gland is absolutely normal in the strict sense of the term; the nodes here included were, however, obtained from individuals either clinically well or suffering from a localized disease at a distant point, and the glands themselves were not enlarged and were essentially normal histologically. The second group consists of enlarged glands gathered from a considerable variety of diseased conditions.

TECHNIC

The material was obtained under the most careful aseptic precautions and, except in two cases, was planted within one hour of removal from the body. In no instance did over twelve hours elapse. A method of maceration was used essentially similar to that described by Rosenow,[8] the steps in the process being briefly the following:

> First, the material was washed through several changes of sterile salt solution, to get rid of blood and possible surface contaminations; it was then dipped in boiling salt solution, to further sterilize the surface, the length of immersion varying with the size of the piece of tissue. Next, it was ground up in a sterile box, suspended in a tube of sterile salt solution, and the resulting mixture added in varying amounts to the mediums. Blood-agar and Loeffler's serum, aerobic and anaerobic, and ascites-dextrose-agar shake tubes were used. The ascitic fluid was heated at 66 C. for twenty-four hours, and stored in lots of 20 c.c., each lot being controlled at the time of culture by several uninoculated tubes.

It seemed that a procedure of so many steps as this one might lead to frequent contaminations. A number of pieces of sterile potato were, therefore, run through in exactly the same way as the glands. It was found that the risk of contamination was about the same as that involved in the usual technic of transfer from tube to tube.

The cultures were all kept at least three weeks before being discarded. The number of colonies, their time of appearance, and general characteristics were noted, and subcultures made both aerobically and anaerobically on various mediums. In nearly all cases a portion of the gland was studied histologically, the interpretation being made in the pathologic department of the Johns Hopkins Hospital.

RESULTS

Thirty-two glands were studied; they may be divided as follows:

I. "Normal" group. (Seven cases.)
- Glands from individuals clinically well..... 2
- Glands from patients with arthritis, but not associated with an involved joint..... 4
- Gland from periphery of a carcinomatous mass in neck — histologically normal 1

II. Pathologic group. (Twenty-five cases.)

Hodgkin's disease	6
Carcinoma	6
Lymphosarcoma	3
Chronic infectious arthritis	3
Tuberculous adenitis	2
Subacute adenitis	2
Gaucher's disease	1
Acute leukemia	1
General glandular enlargement of obscure origin	1

The results have been classified from a number of points of view with reference to the simple presence or absence of organisms.

1. Size.—The glands varied roughly from 0.5 cm. to 3 cm. in diameter. Success in the cultivation of organisms bore no relation to size, the largest being sterile, and some of the smallest yielding as many as 1,000 colonies. The effect of Roentgen and radium therapy, of tuberculous softening, and of carcinomatous induration must be discounted in this consideration.

2. Duration of involvement.—This was in most cases hard to determine with any degree of certainty, but varied certainly from three weeks to three years. No relation could be made out between the extent of invasion and the duration of the disease.

3. The special area or lesion drained.—Only in isolated cases could this be correlated with the bacteriologic results.

4. The location of the gland bore no obvious relation to sterility, as may be seen from the following schema:

Location of Gland	Organisms Obtained in	Organisms Not Obtained in
Cervical (15 cases)	9	6
Inguinal (8 cases)	4	4
Axillary (4 cases)	4	0
Scapular (2 cases)	1	1
Epitrochlear (1 case)	1	0
Supraclavicular (2 cases)	2	0

5. The diagnosis.—In this series a larger number of positive cultures was obtained from the definitely diseased glands than from those approaching nearer the normal, the percentage for the two groups being practically reversed:

	Organisms Obtained in	Organisms Not Obtained in
Hodgkins's (6 cases)	5	1
Carcinoma (6 cases)	4	2
Lymphosarcoma (3 cases)	2	1
Chronic infectious arthritis (3 cases)	3	0
Tuberculous adenitis (2 cases)	1	1
Subacute adenitis (2 cases)	2	0
Gaucher's disease (1 case)	1	0
Acute leukemia (1 case)	0	1
General glandular enlargement (1 case)	1	0
	19 (76%)	6 (24%)
"Normal glands" (7 cases)	2 (29%)	5 (71%)

From this analysis little information is to be gained further than that about two-thirds of the nodes contained organisms, the larger percentage of positive cultures being from the outspokenly diseased glands. The characteristics of the organisms, however, seem to throw them into several distinct groups:

Group I.—Organisms which are to be correlated with the saprophytes on the body surfaces.

These organisms are aerobic, they occurred quite frequently in glands of all sorts, usually in small numbers (less than ten colonies to the gland in all but one case), were avirulent for rabbits, guinea-pigs and mice, and gave no immunity reactions with the patients' serum. They were encountered eleven times in a variety of conditions, including Hodgkin's disease, lymphosarcoma, carcinoma, and in "normal" glands. Typical white staphylococci were identified eight times, and a spore-bearing bacillus, a sarcina lutea, and a pseudodiphtheria bacillus, each once.

They occurred at times alone, but often with the organisms of Group II.

Group II.—Under this heading will be described two types of organisms notable by their frequent occurrence in these cultures, by their presence often in large numbers, and in pure culture, and by a characteristic relation of growth to oxygen tension.

The first type is a short pleomorphic bacillus, which appeared in cultures in from two to twelve days. Growth developed only in "partial pressure" tubes of ascites-dextrose agar, and was limited to the lower portions of the tube, in no case approaching nearer than within 1 cm. of the surface. The original colonies appeared as minute grayish or flesh-colored dots, some having a triangular or pyramidal shape, and reaching a maximum size of from 1 to 2 mm. in diameter in from ten days to two weeks. The rate and level of growth of various strains has been quite constant, and attempts to obtain surface cultures, either aerobically or anaerobically, have all failed. One strain has now been frequently subcultured over a period of twelve months, without inducing any change in these characteristics. The organisms are gram-positive, nonacid-fast, and stain readily with the aniline dyes. The younger cultures show mainly slender, rather short rods, usually smaller than true diphtheria bacilli, some straight and some slightly curved. No polar bodies can be definitely demonstrated, although occasionally the ends appear slightly expanded. Variations are seen from this type to that of a short, stubby bacillus, usually in pairs, which becomes the predominating form in older cultures. No beaded, clubbed or bizarre forms have been seen. In smears, the organisms tend to group themselves somewhat like diphtheria bacilli.

They are nonmotile. The older cultures have a characteristic pungent, sour odor.

Ten strains of this organism have been isolated from twenty-five abnormal glands, the distribution being the following:

Diagnosis	Cases	No. Colonies
Carcinoma	4	75, 25, 2, 2
Hodgkin's disease	2	1,000, 1
Lymphosarcoma	2	150, 1
Arthritis	2	300, 2

In four instances, another type of organism was isolated, which showed the same peculiarities of growth level as the bacillus described above. The colonies appeared in ascites-agar tubes in from two to five days, sharply limited to the subaerobic level, as discrete white pinpoint disks, which were composed of gram-positive cocci, about the size of the usual skin cocci, but differing from them in the early appearance of variations in size, which was always striking by the time the colonies were large enough to be fished. In subcultures they selected the same level, and thus far, it has been impossible to grow them, either aerobically or anaerobically, on the surface of plain, glucose, ascites, or blood-agar, Loeffler's serum, in fluid mediums, or in simple dextrose-agar stabs.

This organism was first isolated from a cervical gland, in a case of acute Hodgkin's disease, the total duration from onset to death being only six weeks. The culture was made three weeks before death, and yielded the organism in pure culture, the colonies numbering about two hundred. A left cervical gland from the patient in a second case of typical Hodgkin's disease of about six months' duration yielded seven colonies of this coccus, with three colonies of a spore-bearing bacillus. A gland removed later from the other side showed the coccus in pure culture. In these two cases, then, the possibility arises of some special conditions favoring the invasion by this organism.

Finally, in a case of lymphosarcoma, it was recovered from a cervical gland, together with the "diphtheroid" bacillus described above.

Whereas the organisms included under the first group are obviously saprophytic and accidental, the significance of these two types does not seem so clear. Their presence in glands, often in pure culture and in large numbers, their constant peculiarities with regard to oxygen tension, raised the question as to whether they might bear more than an accidental relation to the conditions in which they were found. That they were not the specific cause of any one disease seemed established at the start by their occurrence in such a wide variety of conditions.

The virulence of all fourteen strains was tried out on mice, guinea-pigs and rabbits. The growth from two well-grown agar tubes was selected as the dose for a rabbit, one-half this amount for a guinea-pig

and one-fourth for a mouse. It seemed that these quantities were sufficient to test susceptibility, whereas, larger doses might produce nonspecific effects. The inoculations were made intravenously, intraperitoneally, and subcutaneously. No specific lesions or general intoxications developed; the animals were, apparently, quite unaffected. It was noted that, after the subcutaneous injection, not even a local infiltration developed; there seemed to be no irritation or reaction. In two of the guinea-pigs, small temporary enlargement of the inguinal glands appeared after about a week, and then gradually subsided. The organisms could not be recovered from these glands. A monkey received repeated injections, into the axillary tissues, of large amounts of one of the "diphtheroid" strains; a temporary regional adenitis followed; the animal at no time seemed ill, and is now well after an interval of eight months.

In most of the cases, agglutination and complement-fixation tests were made with the patients' serums. The results were negative except with two of the anaerobic coccus strains, which fixed complement strongly with the serum of the patient in the case of Hodgkin's disease, from which one of them was isolated. Such a reaction is, perhaps, of similar significance to positive fixations with colon bacilli, certain streptococci, and other avirulent organisms.

Finally, injections of autogenous vaccines were given in five cases—two of Hodgkin's and three of infectious arthritis—not so much as a therapeutic procedure as to observe the reactions which might be set up. At least three subcutaneous injections at intervals of from four days to a week were made in each case. No effect, beneficial or deleterious, was observed. It was striking here also that large doses—ten thousand million and more—produced not even a local reaction; there was no tenderness, redness or induration.

In summary, then, these organisms seem to be parasitic but nonpathogenic; possibly certain types of gland lesion furnish a soil suitable for invasion by them.

Group III.—Herein are included several isolated observations. From the inguinal gland of a child with a generalized, not suppurative, adenitis of probable cervical origin, were cultivated countless colonies of a typical hemolytic streptococcus of high virulence for rabbits. A week later, at a time when the process was subsiding, an axillary gland yielded about one hundred colonies of a white staphylococcus, no streptococci being obtained. A cervical node from a child with Gaucher's disease, showing typical histologic changes, yielded thirty colonies of staphylococcus aureus. This infection probably originated from an otitis media. Finally, from a gland in an atypical case of chronic arthritis, with splenomegaly, general adenitis, and leukopenia,

there were grown countless colonies of a chromogenic (yellow), small gram-positive diplobacillus, nonvirulent for small animals, but agglutinating and fixing complement with the patient's serum. This organism was encountered only in this instance.

CONCLUSIONS

It is clear, even from this small series of gland cultures, that the findings vary in significance in different cases. In view of the variety of organisms found, it seems that extreme conservatism should be maintained in interpreting any one as the etiologic agent of a specific disease. The following conclusions may, perhaps, be drawn:

1. As indicated by previous work, organisms can frequently be cultivated *intra vitam* from lymphatic glands.

2. There is a higher proportion of successful cultures from definitely diseased glands than from those approaching a normal condition.

3. Saprophytic organisms identical with or closely allied to the surface flora of the body are frequently filtered out, or, perhaps, constitute a more or less permanent flora of lymph glands.

4. Organisms are frequently isolated which seem by their biologic characteristics to be suited to live in relatively avascular areas, and which may tend to invade diseased glands, although they are not limited to them.

5. None of the twenty-nine strains isolated in this series could be shown to be the cause of specific diseases.

STUDY OF A CASE OF PAROXYSMAL HEMOGLOBINURIA

SERUM REACTIONS: UROBILIN AND HEMOGLOBIN EXCRETION *

CHARLES C. DENNIE, M.D., AND OSWALD H. ROBERTSON, M.D.
BOSTON SAN FRANCISCO

The uncertain nature of the hemolytic reaction characteristic of paroxysmal hemoglobinuria presents a problem of continued interest. The majority of investigators are agreed that the theory originally put forward by Donath and Landsteiner[1] explains in a general way the mechanism by which a paroxysm is brought about. But concerning the number and character of the different factors involved and the physical conditions under which they act, there are almost as many opinions as there are writers.

The first part of the paper is a study of this reaction. The second part deals with the quantity of blood destroyed during an experimental exposure to cold and the rapidity of the consequent excretion of hemoglobin by the kidneys.

As the literature contains many clinical descriptions of this condition, only a short history will be given and enough of the physical findings to establish the diagnosis and corroborate the data given by other investigators.

History and Physical Findings.—C. S. R., boy, aged 12, colored, entered South Medical Service of the Massachusetts General Hospital, Nov. 18, 1914. Father and mother, three sisters and three brothers well. His mother has had no miscarriages. No history of syphilis obtainable. The patient had "rheumatism" from the age of 6 months to 3 years. Ever since the age of 3 he has had frequent attacks of hematuria, which occurred only during the winter following exposure to cold. The attack is often accompanied by a chill and followed by fever and pain in the stomach, without subsequent weakness. The hematuria never lasts more than a day. For the past six months he has been gradually losing his eyesight, first of the right, later of the left eye.

Physical Examination: The boy is undersized and only fairly nourished. Intelligent. Forehead bulging. Interstitial keratitis of both eyes. Teeth suggestive of Hutchinsonian type. Scaphoid scapulae. No glandular enlargement. Spleen and liver just palpable. Both shins show a definite periostitis. There is an effusion into all the large joints. The elbows show a slight limitation of motion.

Blood Examination: Red cells, 4,512,000. White cells, 10,000. Hemoglobin, 81 per cent. (Sahli). Differential count, neutrophils 82 per cent., basophils, 17 per cent., mast cells, 1 per cent. Red cells of normal appearance.

---

* Submitted for publication April 28, 1915.

* From the South Medical Department and the Pathological Laboratory of the Massachusetts General Hospital.

1. Donath and Landsteiner: Ztschr. f. klin. Med., 1906, lviii, 173.

Platelet count, 345,000. Coagulation time (method of Lee and White,[2]) nine minutes — upper limit of normal. Wassermann strongly positive. Urine negative except for hemoglobin after paroxysms, never bile, blood, casts or albumin.

PART I: SERUM REACTIONS

In view of the suggestion of all those who have worked with the serums of patients suffering from paroxysmal hemoglobinuria, the blood removed for experimentation in this case was kept at a temperature of 37.5 C. until ready to be chilled. The same precaution was taken with all other serologic material and organic extracts. For the sake of space and convenience certain symbols are used in our work:

N. H. Sr.	Normal human serum.
Pt. Sr.	Patient's serum.
Pt. Ch. Sr.	Patient's serum which has been chilled with patient's red blood cells at 0 C. for one-half hour, centrifuged at the same temperature and the clear serum withdrawn.
Pt. R. B. C.	Patient's red blood cells.
Pt. W. R. B. C.	Patient's washed red blood cells.
N. W. R. B. C.	Normal washed red blood cells.
S. W. R. B. C.	Sheep's washed red blood cells.
G.-P. Sr.	Guinea-pig serum.
R. Ambo.	Rabbit amboceptor.
In. H. Sr. Anti.	Inactivated human serum anticomplementary.
C.	Complete hemolysis.
Ac.	Almost complete.
Pr.	Partial hemolysis.
Tr.	Trace.
0	No hemolysis.

The first experiment consisted of the quantitative demonstration of the autohemolysin and of the native complement, which varied slightly from day to day (Table 1).

TABLE 1.—QUANTITATIVE DEMONSTRATION OF AUTOHEMOLYSIN AND OF NATIVE COMPLEMENT. EXPERIMENT 1 A

Pt. Sr. +	P. W. R. B. C. 10 % Susp.	Result After 30 Min. at 0°, Followed by ½ Hour at 37.5°C.
c.c.	c.c.	
0.4	0.25	C.
0.2		C.
0.1		Ac.
0.05		Pr.
0.025		Pr.
0.0125		Tr.

EXPERIMENT 1 B

Pt. In. Sr. +	Complement +	Pt. W. R. B. C.	Result After 30 Min. at 0°
c.c.	c.c.	c.c.	Followed by ½ Hour at 37.5° C.
0.2	0.2	0.25	C.
0.2	0.1	0.25	C.
0.2	0.05	0.25	C.
0.2	0.025	0.25	Pr.
0.2	0.0125	0.25	Tr.
0.2	0.00625	0.25	0

2. Lee and White: Am. Jour. Med. Sc., 1913, clxxii, 495.

Experiment 1 A shows that 0.2 c.c. of patient's serum is just sufficient to completely hemolyze 0.25 c.c. of patient's washed red blood cells.

Experiment 1 B shows that the amount of native complement present in 0.2 c.c. of patient's serum is equal to 0.05 c.c. of guinea-pig serum.

It has been stated by many observers, Meyer and Emmerich,[3] Donath and Landsteiner, Cook[4] and others, that the hemolytic amboceptor unites with the patient's red blood cells at 0 C. in the absence of complement, then if complement is added later and the test is incubated at 37.6 C., hemolysis results. We were unable to confirm this observation. We found that all the different elements must be present throughout the whole reaction, that is, at the low temperature as well as the subsequent incubation at 37.5 C., or hemolysis does not take place. This is shown by the experiments recorded in Table 2.

TABLE 2.—Experiments Showing that Hemolysis Does Not Occur Unless All Elements Are Present

Pt. In. Sr.	+ Pt. W. R. B. C. 10% Susp., c.c.	Result after 0° for ½ Hour, then Warmed to 37.5° C., and 0.05 c.c. Compl. Added, and Incubated for 1 Hour.
0.4	0.25	0
0.2	0.25	0
0.1	0.25	0
0.05	0.25	0
0.025	0.25	0
0.0125	0.25	0

After the complement was added to each of the tubes previously warmed to 37.5 C. and kept at 37.5 C. for one hour, no hemolysis took place. Each element in turn was left out with the same result. If the complement is added to the tubes before they are warmed up to blood heat, strong hemolysis occurs for the simple reason that the union of these elements takes place in a few minutes in the cold, not necessarily at 0 C. It is obvious that it will require several minutes after the tubes have been placed in the incubator at 37.5 C. to raise the temperature from 0 to 37.5 C. Thus, we found that in our experiments all elements must be present at a temperature below 37.5 C. in order that hemolysis might occur. This result agrees with the findings of Moss[5] and Hoover and Stone.[6]

Again, it is asserted by other investigators, Widal, Abrami and Brissaud,[7] that there exists in the serum of patients suffering from

3. Meyer and Emmerich: Deutsch. Arch. f. klin. Med., 1909, xcvi, 287.
4. Cook: Am. Jour. Med. Sc., 1912, cxliv, 203.
5. Moss: Johns Hopkins Hosp. Bull., 1911, xxii, 229.
6. Hoover, C. F., and Stone, C. W.: Paroxysmal Hemoglobinuria, The Archives Int. Med., 1908, ii, 392.
7. Widal, Abrami and Brissaud: Compt. rend. Soc. de biol., 1913, lxxv, 502.

paroxysmal hemoglobinuria an inhibitory substance which prevents the union of the hemolytic bodies with the patient's red blood cells at 37.5 C., but which is inactive at lower temperature, thus allowing this combination to take place. It occurred to us that if such an inhibiting substance were present in the serum and could be isolated, it should exert a restraining influence on other hemolytic systems if brought into the proper relations with them. A plan was devised for isolating this substance, if it existed, and using it against the sheep-rabbit hemolytic system. Conceding that this inhibiting element is active at blood temperature and inactive at lower temperatures, it should remain free in the centrifuged fluid if the hemolytic amboceptor is given a chance to unite with the patient's red blood cells in the cold. This we attempted to do in the following experiments:

Two c.c. of patient's serum plus 0.25 c.c. of patient's washed red blood cells 100 per cent. suspension was chilled for one-half hour at 0 C., centrifuged at the same temperature and the clear supernatant fluid withdrawn. This fluid should now contain the hemolytic inhibiting bodies free in solution, and if used against the other hemolytic systems might reasonably be expected to prevent their union. We were fortunate enough to have the serum of a patient which at this time and many times previously contained a serologic substance occurring in a sufficient amount in 0.2 c.c. of serum to prohibit absolutely the hemolysis of sheep's washed red blood cells by sensitized rabbit's serum, and this was used as a control in the experiment given in Table 3. For the sake of convenience the control experiment will be given first.

TABLE 3.—Control Experiment

In H. S. Anti. c.c.	+ 5% Susp., S. W. R. B. C. c.c.	Result After Adding 1 Unit R. Ambo. and Incubating ½ Hour at 37.5°	Result After Adding 0.05 Compl. and Incubating 1 Hour at 37.5 C.
0.4	0.5	0	0
0.2	0.5	0	0
0.1	0.5	0	Sl.
0.05	0.5	0	Pr.
0.025	0.5	0	Str.
0.0125	0.5	0	C

Before the complement was added, the tubes were incubated for one-half hour at 37.5 C. There was no hemolysis at the end of this time (which was to be expected). This merely demonstrates the absence of complement. After the complement was added and the tubes incubated for one hour, 0.2 c.c. of this so-called anticomplementary serum was sufficient to prevent completely the hemolysis in the sheep-rabbit system. Smaller amounts allowed some hemolysis to take place for the reason that the anticomplementary substance was present in very small amounts. The serum used as a control had no natural

sheep's red blood cell hemolysins, while the blood of the patient did contain such substances.

The foregoing experiment was repeated, the supernatant fluid removed from the cold-warm experiment being used instead of the anticomplementary serum.

TABLE 4.—Experiment to Show the Absence of Inhibitory Bodies

Pt. Ch. Sr. c.c.	W. S. R. B. C. + 5% Susp. c.c.	Result After Adding 1 Unit R. Ambo. and Incubating ½ Hour at 37.5°	Result After Adding 0.05 c.c. Compl., Incub. 1 Hour at 37.5 C.
0.4	0.5	0	C
0.2	0.5	0	C
0.1	0.5	0	C
0.05	0.5	0	C
0.025	0.5	0	C
0.0125	0.5	0	C

The complete hemolysis in all the tubes at the end of an hour demonstrated that the supernatant fluid used possessed no inhibiting properties. This evidence was further supported by the fact that the patient's serum possessed a very strong natural hemolysis for sheep's washed red blood cells which was in no way affected by these supposedly inhibiting substances.

From these experiments we must conclude that if there is a restraining substance present in the serum of hemoglobinurics which prevents the uniting of the specific substances at body temperature, it does not act in the same way on other hemolytic systems, since it did not in the least prevent the complete hemolysis of sheep's washed red blood cells by sensitized rabbits serum. On the other hand, 0.2 c.c. of a serum containing a known inhibitory substance did absolutely prevent the hemolysis of sheep's washed red blood cells. Furthermore, such a restraining substance did not exist in the serum of the patient suffering from paroxysmal hemoglobinuria. The physical and chemical composition of the autohemolytic amboceptor was such that it would not unite with the patient's washed red blood cells except it first be subjected to cold.

PART II: UROBILIN AND HEMOGLOBIN EXCRETION

It has been shown by several investigators (Wilbur and Addis,[8] Eppinger and Charnas[9] and by one of us[10]) that the quantity of urobilin in the stool may be taken as an index of blood destruction. Blood destruction is greatly increased in diseases which show an abnormal amount of hemolysis going on in the body, as pernicious anemia, congenital hemolytic jaundice, etc. Quantitative estimations for uro-

8. Wilbur, R. L., and Addis, Thomas: Urobilin: Its Clinical Significance, The Archives Int. Med., 1914, xiii, 235.

9. Eppinger and Chamas: Arch. f. klin. Med., 1913, lxxxiii, 387.

10. Robertson, O. H.: The Archives Int. Med., to be published.

bilin[11] were made on the stools of this patient with the expectation of demonstrating an increased output following each paroxysm. Much to our surprise, there was practically no change in the quantity of urobilin excreted during two weeks in which he was given three exposures to cold, all of which were followed by hemoglobinuria. The absence of any increase could be explained in only two ways: first, that the amount of blood hemolyzed at each exposure was comparatively small, and second, that the kidney threshold for hemoglobin was very low, thus permitting a rapid excretion of this substance.

In order to determine the quantity of free hemoglobin in the blood serum and urine, a colorimetric method with a standard solution of hemoglobin was used. The standard solution, that is, one containing a known quantity of hemoglobin, was made by adding 10 c.c. of fresh blood to 100 c.c. of tenth-normal hydrochloric acid, which changed the oxyhemoglobin completely into hematin hydrochlorate, a more stable colorimetric solution. It was then diluted up to 1,000 c.c. with distilled water, thus producing a color suitable to work with. Finally the solution was centrifugated clear. The amount of hemoglobin per cubic centimeter of solution was determined in the following way: Sahli's hemoglobinometer was originally made up by using the blood of one or several individuals whose hemoglobin was 17.2 per cent. of the total blood weight. Thus a blood reading 100 per cent. on the Sahli scale would have 17.2 gm. of hemoglobin per hundred grams of blood. The patient from whom the blood for the standard was taken had a hemoglobin of 40 per cent.; therefore each hundred c.c. would contain 40 per cent. of 17.2, or 6.88 gm. Ten c.c. would contain 0.688 gm., and when diluted to 1,000 c.c. each cubic centimeter would contain 0.000688 gm. of hemoglobin.

The experiment was carried out as follows: Both feet and half the lower legs were immersed in ice water for five minutes. After eight minutes, 10 c.c. of blood were withdrawn from an arm vein into 1 c.c. of 1 per cent. sodium oxalate solution. The boy was urged to micturate every few minutes. After forty minutes he had a slight chill and passed a few drops of deeply blood-tinged urine. Ten c.c. more blood were then taken. The blood in each instance was kept at body temperature from the time it left the vein until the serum had been separated from the corpuscles by centrifugation. This precaution was observed in order to prevent further hemolysis due to cooling. The second specimen of serum was much more deeply tinged with hemoglobin than the first, which was accordingly discarded. Two hours after the exposure to cold, he passed 23 c.c. of purplish-black urine. During the next two and a half hours he was given three

11. The method used was that of Wilbur and Addis (Footnote 8).

glasses of water in order that all hemoglobin might be washed out of the bladder. At the end of this time he passed 100 c.c. more urine only slightly blood tinged. That this was the last specimen to show any hemoglobin was indicated by the fact that a clear urine giving a negative guaiac test was obtained at each later passage.

To the blood serum were added 3½ times its volume of tenth-normal hydrochloric acid, which was quite sufficient to change all the oxyhemoglobin into hematin hydrochlorate. The mixture was next centrifugated to throw down any suspended material. It was then read against a 1:2,000 dilution of the standard solution. After the addition of a few drops of lead acetate to each of the two separate specimens of urine, they were filtered. In this way all organic matter except hemoglobin was removed. Then, in order to insure against any loss of hemoglobin, the precipitate was washed with tenth-normal hydrochloric acid in a quantity equal to three or four times the amount of urine, and these washings added to the urine just filtered. Each urine solution which was quite clear was then read against a dilution of the standard solution somewhere near its color.

It was found that each cubic centimeter of the boy's blood contained 0.000592 gm. of hemoglobin, and this multiplied by his total blood volume, which was estimated at 1,507 c.c., using 1:19 as the ratio of blood weight to body weight, gave a total amount of 0.862 gm. The first specimen of urine contained 0.79 gm., which represented the hemoglobin excreted in the first two hours. The second specimen contained 0.04 gm., representing that excreted during the next two and one-half hours. The sum of the two, 0.83 gm., gives the total quantity of hemoglobin excreted in four and one-half hours. Calculating it in per cent., we find that he excreted in the first two hours 91.7 per cent. of the entire hemoglobin set free, and in four and one-half hours, 96.3 per cent.

It was also very simple to estimate just how much blood 0.862 gm. of hemoglobin represented. His blood showed a hemoglobin of 81 per cent.; using the Sahli scale again, 81 per cent. of 17.2 equals 13.9; that is, each 100 c.c. of blood contains 13.9 gm. of hemoglobin, 1 c.c. containing 0.139 gm., $0.862 \div 0.139 = 6.3$ c.c. of blood hemolyzed.

This exceedingly rapid excretion of hemoglobin accounts for the low urobilin output by the fact that the liver is given very little opportunity to transform the circulating hemoglobin into bile, which is in turn broken down in the intestine into urobilin. Even if the hemoglobin had not been excreted so rapidly, it is questionable whether the relatively small amount of hemoglobin set free would have produced a noticeable change in the amount of urobilin in the stool.

The apparent marked hemoglobinuria can be explained in the same way, namely: by the very low kidney threshold for hemoglobin and its prompt excretion. The small amount of blood destroyed by the short but intense experimental exposure demonstrates that he could stand a great deal of cold without danger to life.

We realize that this method had its sources of error, the chief one being that it was impossible to judge the exact time after the paroxysm when the concentration of hemoglobin in the blood serum would be at a maximum. The time chosen may have been a little late, and some of the hemoglobin may have been excreted already; but as far as we could tell, he had excreted only a very small amount. We did not feel justified in bleeding him oftener at this time.

SUMMARY

The patient was a congenital syphilitic with characteristic physical findings and a strongly positive Wassermann.

The patient suffered from paroxysmal hemoglobinuria with typical attacks following exposure to cold.

These attacks could be induced at any time.

The characteristic hemolysis occurred under proper conditions in the test.

It was shown by experiments that the patient's serum, red blood cells and complement must be present throughout the whole reaction, or hemolysis will not take place.

The failure of the hemolytic reaction to take place unless the elements are first chilled together is not due to an inhibiting substance which is active at blood temperature but inactive in the cold, as the sheep-rabbit system is in no way affected when brought into proper relation with this system. The failure is probably due to the peculiar make-up of the hemolytic amboceptor.

The hematuria following a moderately severe experimental exposure to cold resulted from the destruction of only approximately 6.3 c.c. of blood.

Over 90 per cent. of the hemoglobin set free was excreted in the urine within two hours, and 96 per cent. in four and one-half hours.

The very rapid excretion of hemoglobin by the kidneys probably explains the absence of any increased amount of urobilin in the stools.

A STUDY OF RESPIRATION AND CIRCULATION IN PICROTOXIN CONVULSIONS

THE POSSIBLE BEARING OF THIS STUDY ON THE THEORIES OF PATHOGENESIS OF EPILEPTIC CONVULSIONS *

LEWIS J. POLLOCK, M.D., AND WILLIAM H. HOLMES, M.D.
CHICAGO

The convulsion is the most prominent symptom of epilepsy. It is this symptom which has lent itself most extensively to the study of the pathogenesis of this disorder. There are many phenomena associated with convulsions which have received but scant attention. Chief among these are the circulatory and respiratory disturbances.

In *A Study of Respiration and Circulation in Epilepsy*[1] one of us found that preceding the convulsion in a case of *petit mal,* admirably suited for continuous respiratory and circulatory tracings, a constant series of events occurred (Fig. 1).

A preliminary rise in blood pressure was noticed twenty-six to sixty seconds before the convulsion; when the rise took place over thirty seconds before a convulsion the blood pressure usually fell again slightly. Immediately preceding the convulsion by from nine to twelve seconds there was a sudden marked drop in blood pressure, which remained relatively low during the time occupied by the *petit mal* attacks.

Two seconds later the aura occurred. A period of apnea which preceded the convulsion or its equivalent then followed in from four to nine seconds.

From the facts that respiratory and circulatory disturbances preceded the convulsion or equivalents, the conclusion was reached, that in some cases of *petit mal,* the site of discharge is in the medulla and pons, and furthermore that the medulla and pons participate in the discharge in all cases of epilepsy whether this discharge originates there or not.

If convulsions which are caused by a discharge in the medulla and pons are accompanied by a train of circulatory and respiratory symptoms, it would seem likely that these symptoms should be present in a convulsion artificially produced by a medullary convulsant.

---

* Submitted for publication April 21, 1915.
* Read before the Chicago Neurological Society, March 18, 1915.
* From the Departments of Neurology and Pathology, Northwestern University Medical School.
1. Pollock, Lewis J., and Treadway, W. L.: A Study of Respiration and Circulation in Epilepsy, THE ARCHIVES INT. MED., 1913, xii, 445.

In this paper we wish to describe the circulatory and respiratory changes accompanying the convulsions produced by the administration of picrotoxin.

Picrotoxin is the active principle of *Cocculus Indicus,* or fish berry. It is a medullary convulsant (Roeber[2]). The data tending to uphold this contention will be reviewed briefly below.

Its action along with coriamyrtin, is analogous to toxiresin and digitaliresin (Perrier[3]).

The description of the action of picrotoxin, will be limited to the convulsions, and its effects on the autonomic nervous system.

The convulsion resulting from the administration of picrotoxin has been recognized as being very similar to that observed in epilepsy, by many workers. It will be but briefly described. You may refer to a classical description by J. Crichton Browne.[4]

Following an injection of picrotoxin in a dose sufficient to produce convulsions without causing death (2 c.c. of 4 per cent. alcoholic solution), the animal after a period of time, in which vomiting and sialorrhea may be noted, becomes quiet; sits in one place, and does not respond to calls. Then follows a period of unrest and apparent apprehension. The animal begins to tremble in fore or hind legs, or both, and lies on his side, at times trying to stand erect. Light twitches of face and neck muscles occur becoming stronger and stronger; the head is drawn backwards on the neck. Then immediately there follows a generalized clonic convulsion with clonic champing of the jaws, closing of the eyelids, marked frothing at the mouth, and involuntary urination. During the convulsion the pupils are dilated. The clonic convulsive movements imperceptibly change to running movements of the fore and hind legs, become slower and slower, and finally cease. The animal now remains quiet, lying on his side, and after some effort regains the erect position. After a period of time, varying with the size of the dose, another convulsion occurs.

It is generally admitted by pharmacologists that picrotoxin is a medullary convulsant. Adverse contentions, however (Bechterew,[5] Browne[4]), have not been replied to adequately.

In the pharmacologic sense, convulsions are not clearly defined. They include many spasmodic movements, tremors, twitchings, and tetanic contractions. The pharmacologists have ignored, to a great extent, the work of other departments in pathologic physiology in the

2. Roeber: Physiologische Wirkungen des Pikrotoxins, Arch. f. Anat. u. Physiol., 1869, p. 38.
3. Perrier: Toxiresin, etc., Arch. f. exper. Path. u. Pharmakol., 1875, iv.
4. Browne, J. Crichton: Brit. Med. Jour., 1875.
5. Bechterew: Functionen der Nervencentra, 1908, vi, 187.

study of convulsions. The difficulty in correlating pharmacologic data with that obtained by neurologists and physiologists can therefore readily be seen.

On the other hand, the neurologists who have attempted to prove that the medulla and pons are not directly concerned in convulsions, have not taken pharmacologic data into consideration. The results of both must be considered in reaching a correct conclusion.

Roeber[2] and Grünwald,[6] working with picrotoxin, Albertoni[7] with cinchonidin and camphor, and Perrier[3] with toxiresin, digitaliresin, picrotoxin and coriamyrtin, are the principal workers who have attempted to prove that these various agents are medullary convulsants.

Roeber was able to obtain convulsions with picrotoxin after removal of the cerebrum above the medulla. He contended that picrotoxin is a medullary convulsant.

Since the experiments of Perrier are very clearly given we will review those tending to show that the group of toxins above mentioned are medullary convulsants.

From the fact that these substances cause convulsions he concluded that they act on the central nervous system. On what part of the nervous system they act his further experiments show. After removal of the hemispheres above the optic thalami in frogs, convulsions occur following the administration of the poison. After destruction of the thalami and removal of the hemispheres, convulsions still occur. When the medulla is separated from the spinal cord but two twitches of the head muscles occurred. The rest of the body remained at rest. After cutting through the spinal cord above the lumbar region convulsions occurred in the fore part of the animal only. After section of the right ischiatic nerve the right leg did not participate in the otherwise general convulsion. After the destruction of the medulla the animal quickly became comatose with no convulsion whatever.

He therefore concludes that these substances in causing convulsions act on the central nervous system situated in the medulla oblongata.

J. Crichton Browne[4] in a purely theoretic manner combats this idea as follows:

> Because the thumb and index finger may be moved by galvanic stimulation of the median nerve we do not argue that the movements of these parts are not ordinarily controlled by volition, and so because clonic spasms may occur in rabbits by irritation of the medulla after all other parts above the center have been cut off from it, we cannot argue that such clonic spasms may not proceed from the cerebrum when it remains intact.

---

6. Grünwald: Zur Kenntnis des Pikrotoxins, etc., Arch. f. exper. Path. u. Pharmakol., 1909, lx, 249.

7. Albertoni: Arch. f. exper. Path. u. Pharmakol., 1882, xv, 258.

It seems to us that Browne's objection is not applicable at all, for if, in experimental animals, the medulla after stimulation by picrotoxin acted only as a collection of fibers whose function is the conduction of impulses, then similar results would be obtained after section below the medulla, for these same fibers are found in the spinal cord. By this very objection Browne admits that the medulla at least shares with the cerebrum and ganglia a peculiar ability to be stimulated by picrotoxin which is not possessed by the spinal cord. If the medulla alone after stimulation by a drug causes convulsions in no wise different from those which are caused by stimulation of the cerebrum and medulla it is reasonable to assume that the convulsions may originate in the medulla. We must, however, admit that it is experimentally impossible to disprove entirely Browne's theoretic objection because it would necessitate the removal of the medulla and the substitution of some tracts leading from the cerebrum to the cord.

Bechterew[5] has asserted that in his laboratory, after the removal of the hemispheres, clonic convulsions are not caused by the administration of cinchonidin and absinthe, while tonic convulsions occur.

Albertoni[7] in the most careful work recorded found that in dogs after full operative recovery from half section below the optic thalami with ensuing hemiplegia, cinchonidin produced a generalized bilateral convulsion. He further found that after full operative recovery from ablation of the motor cortex, similar generalized convulsions result from the administration of cinchonidin. He states that under these circumstances the convulsions are slightly diminished when camphor is the drug employed.

Grünwald[6] observed typical picrotoxin convulsions in a decerebrated cat and dog.

We have found in two experiments on dogs, to be more fully described later, that in one after a section below the optic thalami with a cautery knife and in the other after removal of the cerebral hemispheres and optic thalami, picrotoxin caused convulsions differing in no wise from those occurring in animals with an intact central nervous system.

We are therefore convinced that there are drugs which are medullary convulsants and that picrotoxin is one of them.

In a work, the significance of which we will emphasize later, Grünwald[6] studied the action of picrotoxin on the autonomic nervous system. He remarked that a review of the literature shows that aside from the production of convulsions and injury to the heart muscle, picrotoxin causes contraction of the pupils (Falck, Roeber, Luchsinger, Perrier, quoted by Grünwald), salivation (Falck, Roeber, Luchsinger, Gottlieb, also quoted by Grünwald), slow pulse (Roeber, Per-

rier, Gottlieb), urinary bladder contraction (Falck, Gottlieb), and erections (Luchsinger). All these disturbances may be attributed to the autonomic nervous system. In his experiments he verified these findings and demonstrated the central action of this poison as follows: After cutting the bladder nerves "no contractions occurred from the administration of picrotoxin."

In a decerebrated cat, poisoned with picrotoxin and showing a vagus pulse, salivation and bladder contractions, these three respective symptoms disappeared on section of the vagus, chorda and pelvic nerves; furthermore these symptoms did not again manifest themselves following a second dose of picrotoxin. After section of the right chorda, and the administration of picrotoxin, there was profuse secretion from the left salivary duct but none from the right. From these experiments he concluded that picrotoxin is a poison acting on the central autonomic nervous system.

We shall now revert to our supposition, that, if the respiratory and circulatory changes associated with a *petit mal* attack are due to a discharge in the medulla then we should find similar respiratory and circulatory changes associated with picrotoxin convulsions.

We shall not burden this paper with lengthy protocols. The experiments were conducted on dogs approximately of the same weight. Ether anesthesia through a tracheotomy tube was employed. The blood pressure was registered by means of a cannula inserted into the carotid artery and connected with a mercury manometer. The respiration was registered from the tracheotomy tube with a Marey tambour attachment. The time of injection of the drug and the beginning of the convulsions was recorded by means of a Du Bois Raymond key and electromagnet. A metronome time marker was employed. The records were made upon a Stoelting kymograph. The picrotoxin was administered as a 4 per cent. solution either intravenously or subcutaneously. The action of the drug is much more rapid and severe when injected intravenously. Of a large number of records of convulsions observed in nine animals, twenty-three have been selected as suitable for study.

The data may be divided into general changes in blood pressure and respiration and the changes associated with convulsions. The general changes will be briefly dealt with. The blood pressure is raised after the administration of picrotoxin. Contrary to the findings of Grünwald we found that in a decerebrated animal the blood pressure did show a rise. A vagus pulse was observed in all cases. Picrotoxin acts as a respiratory stimulant.

With reference to the changes in blood pressure and respiration associated with convulsions, the material may be divided into four groups.

A. Twelve convulsions in three animals following moderate doses of picrotoxin.

B. Two severe convulsions in two animals following large intravenous doses of picrotoxin.

C. Seven moderate convulsions occurring in one animal following a very severe convulsion as the result of a large intravenous dose of picrotoxin.

D. One convulsion in a decerebrated animal.

In Group *A* which we term the typical reaction, we found that the convulsion started with twitching of the muscles, and respiratory irregularity, that preceding these symptoms by from three to ten, usually three to eight seconds, there was a fall in blood pressure which lasted until apnea had occurred. Apnea was concomitant with the severe clonic convulsion and did not precede it.

When respiration continued but was irregular during the convulsion, the blood pressure fell before the convulsion, and commenced to rise about five respirations after the severe clonic convulsion with its accompanying irregular respirations commenced.

In one tracing of Group *B* it was found that the blood pressure rose slightly with the convulsion and was associated with a few muscular twitchings and irregular respirations. A drop in the blood pressure and more marked twitching then occurred, followed by a period of apnea and severe clonic convulsions. The blood pressure continued to fall until almost the end of the period of apnea and then rose again.

In the other tracing of this group no period of apnea was present, and the blood pressure commenced to rise very shortly after the severe clonic convulsions began, having fallen before the convulsion began. It is to be noted that the first tracing of Group *B* is from the same animal that gave the seven tracings in Group *C*.

In Group *C* blood pressure began to fall during the period of apnea and rose during the period of respiration. The convulsion preceded the drop in blood pressure (Fig. 3).

In Group *D* a decerebrated dog, after an injection of picrotoxin developed tetanic convulsive movements, then irregular clonic convulsive movements, and, after a period of quietude a typical tonic-clonic picrotoxin convulsion which ended in running movements. Concomitant with this convulsion there occurred a drop in blood pressure and an increase in the respirations which had been very slow and irregular following the decerebration.

There were no Traube-Hering waves present in any of the tracings. The pulse was slightly increased in rapidity during all convulsions except such as occurred tumultuously where a vagus pulse persisted.

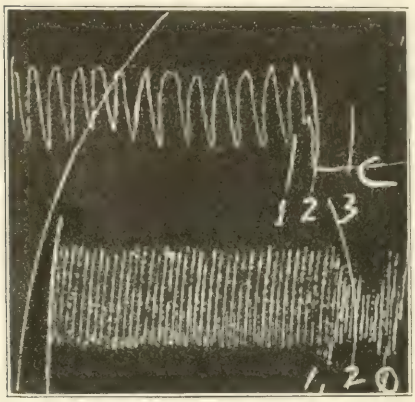


Fig. 1.—1, drop in blood pressure; 2, beginning of apnea; 3, convulsion.

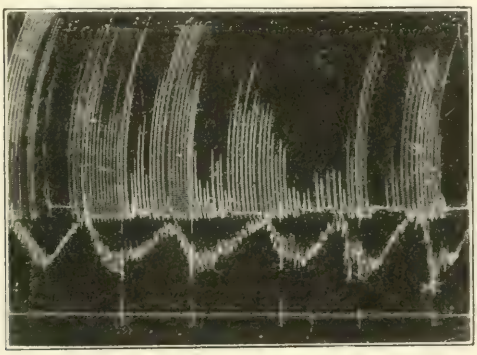


Fig. 2.—Convulsion preceded by drop in blood pressure.

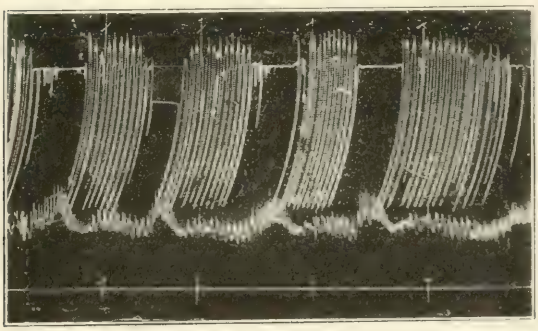


Fig. 3.—Convulsion followed by a period of apnea, during which the blood pressure fell.

From the above facts it may be deduced that the period of apnea does not bear any definite time relation to the drop in blood pressure. In one series the blood pressure began to fall, and in another to rise at the beginning of apnea. When apnea was replaced by shallow irregular respirations the blood pressure showed the same change. We also observed that the degree of blood pressure change is not influenced by the length of apnea, or the degree of respiratory irregularity. The period of apnea when present usually begins with the severe clonic convulsion. The changes in blood pressure, while concomitant with the convulsion, bear no definite time relation to it, neither can they be said to be the cause of the convulsion.

There now remains the interesting observation above noted, that in one series of convulsions the blood pressure rose with the beginning of apnea and fell in another series. In the first the blood pressure fell before the convulsion, in the other the convulsion preceded or was synchronous with the fall. This disparity affords an opportunity for certain definite conclusions. There are but few possible explanations of the cause of the diversity of changes in the blood pressure. The periodic rise and fall of blood pressure may be independent of either the respiratory changes or convulsions. In one series the blood pressure changes are those which regularly precede and accompany the convulsions. In the other series for some reason the blood pressure change may be due only to the period of apnea which results in such a fall of blood pressure as is found in the beginning of the so-called convulsions caused by strychnin, or the fall may be dependent on some change consequent to the convulsion.

In any event one conclusion can be reached. The periodic change in blood pressure is not due alone to either the convulsion or the period of apnea. It occurs in most cases as part of the manifestation of picrotoxin poisoning, and although bearing no time or causal relation to the convulsion, nevertheless occurs about the same time.

The period of apnea can not be so easily explained. It might be the result of the participation of the respiratory muscles in the generalized convulsion. It might be due to the cerebral anemia resulting from the discrepancy of balance between a relatively low general blood pressure and a high intracranial tension (Cushing, Eyster, Pollock). Or it may be due to acapnea, or depression of the respiratory center. Further work must be done to determine the cause.

We must here allude to the statement of Grünwald that the respiratory embarrassment is responsible for the rise in blood pressure in picrotoxin poisoning. While it is true that by the use of artificial respiration he was able to prevent the rise it is true only with regard to the general blood pressure and it is not referable to the changes

about a convulsion. It is remarkable that although the blood pressure changes have been studied extensively in many toxic states, that even in strychnin convulsions the separate phases of blood pressure change associated with a convulsion are not described.

It is generally stated that during a strychnin convulsion blood pressure rises, yet although it does so, suddenly, with the first hard tetanic contraction it drops during the entire period of tetanic apnea and then rises to a great height. This same inaccuracy of observation we have already pointed out in our work on the circulatory and respiratory changes in epilepsy.

It may finally be said that although apnea and definite blood pressure changes occur along with the convulsion caused by picrotoxin, they do not bear the same constant relation to the convulsion as is found in *petit mal* states in man. Yet the independent variation in blood pressure occurring about the time of a convulsion is another proof of the medullary action of picrotoxin, which conclusion has been heretofore supported by its causing medullary convulsions and its action on the central autonomic system. The convulsion of idiopathic epilepsy is made up of a train of symptoms, the motor movements being but one of these.

Respiratory and circulatory changes, salivation, often involuntary urination, at times defecation and perhaps pupillary and thermic changes are as much a part of an idiopathic epileptic convulsion as are the motor disturbances.

Although artificially produced cortical fits may simulate imperfectly some of the motor disturbances of an idiopathic epileptic convulsion, it is only when an "after" generalized convulsion ensues as the result of a long continued cortical irritation, that the remaining symptoms such as salivation, etc., are present. The theory of the cortical origin of idiopathic epileptic convulsions fails, as pointed out by Hirt, to explain the presence of salivation, involuntary urination and respiratory change.

It would seem rather far fetched to search in the cerebral cortex for a center for the origin of these disturbances to place them alongside of Unverricht's area for the production of cessation of respiration and vascular change.

These symptoms may all be attributed to a disturbance of the central autonomic nervous system. They have been observed in picrotoxin poisoning and experimentally proved to be due to the action of this drug on the autonomic nervous system.

Toxic doses of picrotoxin cause not only convulsive motor disturbances but also such other symptoms as salivation, involuntary urination, etc., as are observed accompanying the convulsion of idio-

pathic epilepsy. Although the circulatory and respiratory changes associated with the picrotoxin convulsion are not exactly similar to those found in idiopathic epileptic convulsions, yet the independent presence of blood pressure change associated with picrotoxin convulsions tends to show that these changes are part of the convulsion alike in picrotoxin and idiopathic epileptic convulsions.

From the facts that there exist medullary convulsants and that their ensuing convulsions are associated with symptoms of disturbance of the autonomic nervous system similar to those found in idiopathic epileptic convulsions, and with circulatory disturbances analagous to those found in idiopathic epileptic convulsions, we conclude that we have further evidence that the site of discharge of the convulsion in some types of idiopathic epilepsy is in the medulla and pons. The medulla and pons participate in the convulsion in all cases of epilepsy whether the site of discharge is here or not.

25 East Washington Street.

THE MORE RECENT DEVELOPMENTS IN THE STUDY OF ANAPHYLACTIC PHENOMENA*

HANS ZINSSER
NEW YORK

I

It is a fundamental biological truth that the systematic treatment of an animal with a foreign protein, if this is administered by any route other than that of the alimentary canal, induces profound physiological changes. These changes are primarily recognizable by the appearance in the circulating blood of substances which superficially react with the injected protein. For convenience of discussion we speak of these reaction products as antibodies, and of the injected substances, which possess this power of inducing their formation, as antigens.

Antigens, then, are all substances which injected into the animal body, induce specific antibody formation. They form a large group in nature and are chemically proteins; indeed, we may say that all known proteins may act as antigens. Whether or not this term may also include lipoid-protein combinations, lipoids or the higher protein derivatives is as yet uncertain and need not in the present connection concern us.

We may divide antigenic substances into two main classes. One of these comprises all of those substances of bacterial, animal or vegetable origin which, injected into the animal body, give rise to specific *neutralizing* or *antitoxic* properties in the blood of the injected animal. These are the bacterial exotoxins, the snake venoms, some powerful vegetable poisons and proteolytic and other enzymes of animals and plants. They are all substances which are powerfully active—some of them strongly toxic to the living animal, others true enzymes or ferments. Indeed all of them possess properties which at least suggest our placing them into the class of enzymes in general. The number of such substances known is limited. The reaction they call forth in the animal body seems aimed directly at the specific neutralization of their respective activities, and is so unique and different from that induced by other antigens that it would be convenient had we another term like "antitoxinogen" to set them apart by themselves.

* Submitted for publication Feb. 16, 1915.
* Lecture delivered before the Harvey Society of New York, Jan. 30, 1914.

The other class of antigens comprises all proteins which are inactive, showing in themselves neither toxic nor enzyme-like properties. Introduced into the animal body parenterally, they call forth a response of a nature entirely unlike that of the antitoxins, and which as far as we can fathom its purpose seems aimed merely at the assimilation or the removal of the infected substance. For the cells of the animal cannot utilize the foreign protein as such, and thus it is only foreign proteins injected into an animal that act antigenically and no antibodies are formed when homologous material is injected.

This large group composed of all formed and unformed substances in nature in which a protein structure is involved, does not induce the formation of anything like the neutralizing antitoxins spoken of above. The antibodies appearing in animals treated with such substances have been spoken of as cytolysins or cytotoxins—precipitins—and in the case of formed antigens like bacteria or blood cells—agglutinins and opsonins. It is our opinion that all these various antibodies are identical in structure and significance. The probable identity of agglutinins and precipitins was suggested long ago by Paltauf, and the identity of precipitins with the antibodies which sensitize foreign proteins to the action of alexin or complement has been rendered more probable, we believe, by our own experiments. The terms agglutinin—lysin—precipitin and opsonin are all descriptive of effects produced when an antigen meets its specific antibody. These effects will differ according to the physical condition of the antigen. We believe that it is most likely, both from a study of the work of others and our own experiments aimed at this point directly, that the visible agglutination or precipitation are secondary effects incidental to the colloidal nature of the reacting bodies and to the quantitative proportions in which the reactions occur, the essential process being the union of antigen and antibody, by which the former is rendered amenable to the action of complement (alexin) or leukocyte as the case may be. It is not necessary, at any rate, to assume that functionally there is more than one variety of antibody, this one being the specific sensitizer. However this may be, the definite fact remains that injection of antigens of this second class into animals induces specific reaction bodies or antibodies in the plasma of the treated animal which can be shown to unite with the homologous antigen in vitro, and which probably do so in the body of the animal when the antigen is reinjected into a subject in which antibody formation has taken place.

We must not forget, however, that the observation of antibodies in the circulating blood is but one of the changes that have taken place in the treated animal. Much has been made of this phase of the problem because serum antibodies are readily studied in vitro; but

their origin of course must be sought in the body cell, in which the original and most profound changes must necessarily have taken place during such treatment, changes the nature of which are to a large extent still a mystery, but on which ultimately depend the important physiological difference between treated and untreated animals. For such changes—whether we refer to those immediately under discussion, namely, those of allergy or anaphylaxis, or whether we think of the so-called immunity remaining after attacks of many diseases—remain present long after the circulating antibodies have disappeared and must therefore be regarded as associated with profound alterations in the ultimate tissue unit, the body cell.

Pasteur's observation that animals systematically treated with sublethal doses of bacteria became specifically more resistant to subsequent infection, carries in it all the principles of the process of which we speak as "active immunization," and all the modifications and adaptations to special cases which we now employ are based on this simple truth. The successful transference of such increased powers of resistance to normal animals with the serum of the immunized individual, by Behring and his collaborators, gave us "passive immunization," and these two discoveries are the pillars on which all our complicated subsequent development of details has rested. Since with bacteria and their poisons the process implied the protection of the body against disease or death, we have, rather unfortunately, come to speak of these procedures as "immunization," although the reactions of the animal body to injections of bacteria, reactions on which incidentally the protection depends, are in principle identical with similar reactions resulting from the injection of entirely innocuous substances, such as egg albumin, blood serum or blood corpuscles. It is, therefore, misleading when we speak of the immunization of an animal to, for instance, sheep cells or horse serum. A physiological exchange takes place in such animals entirely analogous with that which occurs in those receiving bacterial protein, but the substances injected are in the former entirely harmless; and indeed, as we shall see, the animal, while entirely immune to large quantities at the first injection, may be severely injured or even killed by subsequent administrations of the same substance. Thus the animal most "immune" to horse serum is the one that has never received an injection of horse serum. It is necessary, therefore, to emancipate ourselves from the misleading elements in the habitual terminology so that we may avoid confusion in grasping underlying principles.

The essential feature common to all antigen injections, therefore, is that of specific antibody formation. That their production in the case of living or dead bacteria—harmful in themselves—protects the

animal from invasion and prevents development and multiplication of the organisms once admitted, though of the greatest practical importance, is purely incidental.

It is not impossible that the physiological reaction indicated among other things by the circulating antibodies denotes a mechanism aimed at the more effective assimilation and elimination of the body-foreign antigens that have been injected, and this, in the case of the bacterial cell, which of course represents a foreign protein, has the effect of protection against invasion. This point of view of the significance of antibodies is the so-called theory of "parenteral digestion" of which we will have more to say directly. We must remember at any rate that in all cases in which, clinically or experimentally, we are confronted with the presence of foreign antigens in the blood and tissues, we are dealing with abnormal conditions in which the mechanism available under normal circumstances for the disposal of foreign proteins which may gain entrance accidentally in extremely minute quantities is under a strain and abnormally active. The extreme quantitative increase of the antibodies is alone sufficient testimony for this, and under the special conditions which we are about to discuss, the repeated introduction of such antigens into the body of an animal in which specific reaction bodies have been induced, whether these are freely circulating or still parts of the cells which produced them, may have illness or even death as a consequence. This is anaphylaxis.

To approach this subject logically without allowing secondary factors to divert our attention from the fundamental principles involved, we should not limit this term to any arbitrarily stated train of symptoms, nor should we attempt too rigidly to limit the definition of what we call anaphylaxis. Indeed, from the point of view of human pathology, it is of quite as much, if not of more, importance to study the effects of slow and slight injuries of this category, than it is to observe them only in the extreme and stormy manifestations of acute anaphylactic death. The former are the types of reactions occurring in the ordinary incidents of life. The latter are extreme results of experimental procedures and are for this reason of course more likely to reveal the underlying principles. But it would lead to false logic in our deductions were we to mistake a difference in degree for a difference in principle.

In the light of our present understanding, therefore, we should broadly define the term as the injury, acute or slow, severe or slight, which under manifold circumstances, may follow on the meeting of an antigen with its specific antibody within the animal body. When such injury fails to result in the case of the spontaneous entrance or the experimental injection of bacteria into an immunized subject it is

probably because the organisms are disposed of before the amount of foreign protein is sufficient to permit such a harmful reaction. What these circumstances are is the problem before us. In the case of innocuous foreign proteins such as blood serum or cells incapable of multiplication, it is doubtful whether immunity—that is, ability to escape harm on reinjection—ever exists. However, we do know that the animal may be nonsensitive, as on first injection when practically no specific antibodies are present, or it may be hypersusceptible, anaphylactic, or (the most comprehensive term) allergic.

II

We may discuss briefly the conditions under which so-called anaphylactic shock may be experimentally elicited in animals. Although of relatively recent development, in their details, the observations which underlie the phenomena took root in the early history of serum investigation. Morgenroth[1] speaks of an observation by Magendie as early as in 1839 in which he describes the sudden death of dogs when repeatedly injected with egg albumin. Flexner reported similar deaths in rabies repeatedly injected with dog serum. Richet and Héricourt[2] in 1898 showed that toxic eel serum injected into dogs would kill at the second injection in far smaller doses than were necessary to kill at the first injection. Similar significance attaches to the work done by Portier and Richet on actinocongestine. Properly belonging in this group of phenomena are the early observations on hypersensitiveness to toxins in repeatedly injected animals made by Behring and his collaborators. The problem was brought into particular prominence by the observations of Arthus[3] in 1903, who found that horse serum injected into rabbits at intervals of several days would eventually, in the later injections, give rise to severe infiltration and edema, and almost at the same time Theobald Smith noticed the great susceptibility to horse serum acquired by guinea-pigs that had been used for diphtheria antitoxin standardization. Independently and with great clearness of vision von Pirquet[4] had made similar investigations on clinical material, and in his work on serum sickness appears to have grasped the fundamental significance of the phenomena with a thoroughness not shared by most of his contemporaries. The historical development of this subject and the experimental conditions under which hypersusceptibility may appear were the subject of a paper read before this society some years ago by two of the pioneer workers in this subject,

1. Morgenroth: Ehrlich Gesammelte Arbeiten, translation, Wiley & Son, New York, 1906, footnote, p. 332.
2. Richet and Héricourt: Compt. rend. Soc. de biol., 1898, xv, 137.
3. Arthus: Compt. rend. Soc. de biol., lv, 817.
4. Von Pirquet and Schick: Die Serumkrankheit, Wien, Deuticke, 1906.

Rosenau and Anderson.[5] The fundamental facts concerning the anaphylactic reaction were worked out almost immediately under the observations of Theobald Smith and Arthus by these workers and by Otto[6] in Germany. I may be permitted to summarize this early work and the fundamental principles of anaphylaxis very briefly in order that we may not spend our time in detailed consideration of facts entirely familiar to most of us.

It is now certain that hypersusceptibility may be produced in human beings, in guinea-pigs, in rabbits, in dogs, in sheep and probably in all mammals, if we were to investigate them carefully.

The condition may be produced by treatment with any of the substances known to us which have the property of antibody production; in other words, with all substances in nature of which we speak as antigens.

The condition is like other antigen-antibody reactions, specific within the limits of specificity recognized for all such reactions. It is certain that in so-called active sensitization, hypersusceptibility develops only after lapse of a definite interval, and this interval depends to a certain extent on the amount administered at the first injection.

An animal once sensitized if not reinjected may remain sensitive for a long period; its sensitiveness will disappear immediately after recovery from a non-fatal reinjection or the animal may temporarily be desensitized by reinjection of the antigen at a period before hypersusceptibility has developed.

Of the greatest theoretical importance furthermore is the fact that a normal animal may be rendered sensitive, passively, by the injection of blood serum from an actively sensitized animal, or by the blood serum of any animal which has been once or repeatedly injected with the antigen; and according to Doerr and Russ and others there is a definite parallelism between the capacity of a serum passively to sensitize an animal, and its contents in specific antibodies.

There are many other facts which are of importance, but which for the present we will neglect, since these are the fundamental phenomena on which we may build our discussion. We may also dismiss very briefly such earlier theories of anaphylaxis as those of Gay and Southard[7] and Besredka,[8] in which attempts were made to show that the substance which sensitizes is not identical with that which is responsible for the development of shock in the reinjected animal. We may, indeed, disregard as premature theories, all those in which the anaphylactic reaction is removed from the sphere of true antigen-antibody reaction. Indeed, von Pirquet and Rosenau and Anderson from the beginning regarded anaphylaxis as the result of the reaction between the reinjected antigen and the antibody formed in response to the first administration; and indeed, this is the essential premise of the still

5. Rosenau and Anderson: Bull. 29, U. S. P. H. S., 1906; Bull. 30, 1906; Bull. 36, 1907; Jour. Med. Research, 1906, xv; ibid., 1907, xvi; Jour. Infect. Dis., 1907, iv; ibid., 1908, v.

6. Otto: Das Theobald Smithsche Phaenomen, etc., von Leuthold Gedenkschrift, 1905, i.

7. Gay and Southard: Jour. Med. Research, 1907, xvi.

8. Besredka: Bull. de l'Inst. Pasteur, 1908, vi, 826.

earlier view of Vaughan. We may accept it at present, identifying the anaphylactic antigen with antigens in general, and the anaphylactic antibody with the protein antibody, not distinguishing for this purpose between agglutinins, precipitins, or cytolysins.

The symptoms which follow on the reinjection of antigen into sensitive animals may show a wide range of variation according to the degree of sensitiveness and amounts injected. In acute anaphylaxis of guinea-pigs, which as you know has been the most thoroughly studied, there is a rapid and severe death which may not occupy more than a fraction of a minute or at most five to ten minutes. The animals repeatedly show restlessness, cough, pass urine and feces, develop severe dyspnea, with infrequent respiration in which there seems to be almost complete immobilization of the chest wall and in which finally only shallow, irregular, spasmodic efforts take place. This, as Auer and Lewis have shown, is due to tetanic contraction of the small bronchioles, with occlusion of the air passages, practically no air entering the lungs. As the dyspnea develops, there may be at the same time spasmodic twitching of the limbs, retraction of the head and general convulsions.

When for some reason or other the reaction is not so severe the animal may show merely general signs of illness, ruffling of the fur, twitching and restlessness, with respiratory difficulty of varying degree, coughing, and evacuation of urine and feces. In rabbits the symptoms are often less rapid in development, but in general principles are similar; in rabbits there is more frequently in the moderate cases a gradual muscular weakness in which the animal lies flat on the ground unable to support itself on its legs, a condition which may proceed for long periods. Death is largely respiratory and the heart may continue to beat for a long time after respiration has completely stopped.

There is a sinking of blood pressure and a depression of temperature.

The coagulation time of the blood is lengthened, there is apparently a depression of the leukocytes, and according to a number of investigators, who have been recently confirmed by Behring, there is a disappearance of blood platelets and an increased flow of lymph.

Pathologically in an animal dead of anaphylaxis there may be petechial hemorrhages, according to Gay and Southard, in the heart muscle, pleura and intestinal wall and there may be fatty degeneration of the vascular endothelium. In guinea-pigs especially there is a marked emphysematous dilatation of the lungs which is very constant, although according to Doerr it is not absolutely characteristic of this condition. Apart from the anatomical changes following acute anaphylaxis, frequently repeated injections of small doses of horse serum or egg white in dogs, cats, rabbits and guinea-pigs have been shown by Longcope to produce cell injury in various organs, especially in the liver, myocardium and kidneys.

The sudden onset, the nature of the reaction in the animal and the pathological lesions seem to indicate that the injury as occurring in anaphylaxis is due to a poison. It appears, then, that an animal is sensitive to a protein at certain stages at which specific antibodies to the sensitizing protein have been formed, and that under special circumstances the meeting of antigen with antibody within the animal, results in a reaction in consequence of which the poisonous substance is liberated. This being the logical point of view on the basis of avail-

able knowledge, it was quite natural that many investigators were attracted by the theory of parenteral digestion.[9]

III

It is one of the earliest premises of Pfeiffer's conception of bacteriolysis that the cell-dissolving action of immune serum liberates a preformed poisonous substance or endotoxin from the bacterial cell. It may be remembered that early in the history of such researches Pfeiffer and some of his pupils showed that an immune animal could be killed more quickly by large doses of dead bacteria than could a normal animal, an experiment from which the conclusion was drawn that the more rapid bacteriolysis in the immunized animal resulted in a more rapid liberation of the endocellular poisons. This point of view has been many times brought forward, and of recent years most clearly by Wolf-Eisner.

It is also a point of view represented by the theory of Nicolle, who similarly tried to explain anaphylaxis by the liberation of poisonous substances from the antigen through the action of the cytolysins or "albuminolysins."

As the investigation of antibody formation against foreign proteins of inherently harmless nature progressed, the belief gained strength that antibodies in facilitating the chemical disintegration of the injected foreign protein represented a sort of emergency apparatus for parenteral digestion and consequent assimilation. Throughout the development of Metchnikoff's ideas of immunity it is plain that he had tended toward such an interpretation, looking on the process of phagocytosis as a method of facilitating the removal of undissolved foreign substances from the tissues and blood, while the serum antibodies were conceived as more particularly concerned with the unformed foreign

9. The curious changes in the coagulation of the blood during the anaphylaxis have led to an interesting and important theoretical conception, namely, that the meeting of antigen and antibody may not, as otherwise believed, lead directly to the formation of a poison, but that in some way the results of such a union may influence the coagulation processes and that these alterations are the direct cause of shock. The first to give serious attention to such a train of reasoning was probably Nolf, and Doerr has recently called attention to the work of a number of investigators (recently confirmed by Moldevan) who observed that freshly defibrinated blood, i. e., blood in which the normal coagulation has been interrupted, may be toxic even when reinjected into the same animal. The same is true of serum taken from rapidly defibrinated blood. There is at least a possibility, then, that the anaphylactic injury is the result of an alteration in the blood indirectly brought about by the union of antigen and antibody. However, the premises for such reasoning are still very vague, and moreover, any view which introduces the various elements which participate in blood coagulating processes can have no part in such manifestations as those observed on isolated and washed tissues, as in the experiments of Schultz and Dale.

proteins which in the accidents of ordinary life gained entrance. The most clear and thorough exposition of such a point is that which since 1907 has been carefully worked out by Vaughan, and to him belongs the credit for the development of many of the ideas underlying prevalent opinions on anaphylaxis. Vaughan, as you well know, subjected many different proteins, bacterial and others, to hydrolytic cleavage in absolute alcohol containing 2 per cent. of hydroxid.

The protein is covered in flasks with 25 to 30 times its weight of this alkaline alcohol and the mixture boiled at 78 C. for an hour or more. In this way he has succeeded in splitting off from a large number of different proteins the toxic fraction.

Since Professor Vaughan[10] himself has but recently embodied his views in a concise treatise, it is quite unnecessary to go into it more than to review briefly his views. He believes that all true proteins contain a poisonous group which is practically the same in all of them. This poison can become free and active when proteins are submitted to various methods of decomposition. Protein sensitization, in other words, is due to the fact that there is developed after the first injection a specific proteolytic ferment, and this on second injection so acts on the reinjected antigen that the toxin fraction is set free and poisoning results. This, in brief, is Vaughan's point of view and is supported, first, by the fact that such poisons can be formed by his chemical methods from many different kinds of protein; and second, that these poisons, whatever the antigen from which they are derived, may produce symptoms which are in many ways identical with those characteristic of anaphylactic shock. Since, as Vaughan states, proteolysis consists in a gradual breaking up of the protein molecule into simpler and simpler groups, there is an increase of poison liberation up to a certain point in the process; but when it has proceeded beyond this the poison itself is decomposed and ceases to have toxic action. Vaughan believes that anaphylaxis in all its manifestations, whether acute or chronic, is merely an incident in parenteral protein digestion. In the course of this when the relation between circulating antigen and the specific enzyme is such that large amounts of the toxic fraction are suddenly liberated, acute shock follows.

It is hardly necessary to call attention to the attractiveness of such a theory, which so simply explains the apparently mysterious conditions prevailing in anaphylaxis, and there seemed to be very little doubt as to its correctness when Friedemann[11] some years later showed that the action of fresh unheated serum (i.e. alexin or complement) on sensitized red blood cells will produce a poison that, injected into

10. Vaughan: Protein Split Products, etc., Lea & Febiger, 1913.
11. Friedemann: Ztschr. f. Immunitätsforsch. u. exper. Therap., 1909, ii.

rabbits, gives rise to anaphylaxis-like shock. Following him Friedberger[12] succeeded in producing a similar poison by allowing fresh guinea-pig serum (i.e., complement) to act on both precipitates formed by the union of the serum with its antiserum and on sensitized and unsensitized bacteria. These investigations clearly suggested that the action of the alexin present in the circulating blood, on an antigen sensitized with its specific antibody, might produce protein cleavage in which there was liberated a toxic fraction similar to that produced by Vaughan with his chemical hydrolytic methods. It is but natural, therefore, that Friedberger, to whom the greatest credit in the more recent development of this point of view belongs, should assume that the poison liberated in this way is the toxic factor concerned in anaphylaxis, and name it "anaphylatoxin." For reasons which will appear directly, we think that a preferable term would be "proteotoxins."

The technic developed by Friedberger consists, in the case of dissolved proteins, in allowing the antiserum to act on the serum until a precipitate is formed, then subjecting this precipitate to the action of fresh guinea-pig serum or complement. After a variable number of hours, the length of time depending on secondary factors, which need not be discussed in describing the process, the centrifugation removes the precipitate, the supernatant guinea-pig serum is found to be strongly poisonous, and injected into guinea-pigs intravenously in quantities of from 2 to 4 c.c. produces symptoms typical of acute anaphylaxis. With bacteria his technic is similar. At first bacteria sensitized with inactive immune serum were subjected to the action of fresh guinea-pig complement for from one to two hours at 37 C. to as long as twelve to twenty-four hours at refrigerator temperature. At the end of this time the bacteria is removed by rapid centrifugation, and the supernatant fluid injected into guinea-pigs produces again typical symptoms of acute anaphylaxis.

The first interpretation applied to these experiments by Friedberger was an entirely natural one if we consider the general views held before this concerning bacteriolytic and bactericidal processes. He assumed that the complement acting on the sensitized bacteria or on the sensitized protein in the precipitate experiment (or later on the unsensitized bacteria), produced proteolytic changes in the course of which the toxic split product was formed. It seemed that the poison was pharmacologically the same whatever the antigen used, and experiments also seemed to show that the poison could be produced more rapidly from strongly sensitized than from unsensitized bacteria, and that an excess of sensitization or a too prolonged interaction resulted in nontoxic supernatant fluids, which was taken to indicate that the protein had been split beyond the toxic stage by too energetic hemolytic action.

12. Friedberger: Berl. klin. Wchnschr., 1910, Nos. 32 and 42; Ztschr. f. Immunitätsforsch., 1910, iv.

Here, then, we have a simple and apparently logical explanation of anaphylaxis, entirely in accord with Vaughan's views of parenteral digestion. An antigen is injected into an animal, specific antibodies and enzymes against it develop in the animal; reinjection of this antigen results in relatively rapid proteolysis in the course of which poisonous substances, the anaphylatoxins, are produced and anaphylaxis is the result. This hypothesis although very attractive does not entirely meet with the facts as they have been developed since Friedberger's first work. The premises on which it is based assume in the first place that the poison or "anaphylatoxin" is formed out of the matrix of the antigen; further, it is definitely assumed that in the production of the poison after the antigen and antibody have met, the complement or alexin plays an active part. Friedberger's hypothesis as stated by him, moreover, seems to assume that the entire process takes place intravascularly, a matter which we will discuss at considerable length in a short time. It is important to note also that Friedberger, with Nathan, was able to show that this anaphylatoxin production could take place within the animal body; that is, within the peritoneum of a guinea-pig into which bacteria had been injected.

The simplicity of Friedberger's explanation and the correctness of his experimental data soon persuaded many investigators that, in essence, his hypothesis probably contained the nucleus of the solution of this difficult problem. However, even his own early experiments aroused some misgivings concerning the matrix of the poisons produced, for he found that the poisons could be obtained as well when boiled antigen was used as when the fresh, unheated substances were employed, and the poisons were easily obtained from such organisms as the tubercle bacillus, which is extremely insoluble and unamenable to serum influence. It was also doubted whether one could truly assume the participation of this specific antibody or sensitizer in the production of Friedberger's poisons, since it soon developed that from bacteria, at least, the poison could be produced when the organisms were directly exposed to the action of fresh guinea-pig serum without the presence of any immune serum.

Experiments which soon threw a definite doubt on the assumption that the poisons were produced by a decomposition of the antigen were reported by Keysser and Wassermann.[13] These workers substituted insoluble substances like barium sulphate and kaolin for the antigen; that is, the precipitates or bacteria used in Friedberger's experiments. They found that if kaolin were treated with horse serum and then exposed to the action of guinea-pig serum or complement,

13. Keysser and Wassermann: Folia serol., 1911, vii; Ztschr. f. Hyg. u. Infectionskrankh., 1911, lxviii.

poisons were produced identical in every respect to those produced by Friedberger's method. The conclusions they drew were that the poisons were produced, not by action of the complement on the antigen, but by its action on the horse serum absorbed by the kaolin. In other words, they transferred the matrix of the poison from the antigen to constituents in the serum itself, possibly the sensitizer or amboceptor. Bordet[14] also was able to show that poisons similar to those of Friedberger could be produced by the action of fresh guinea-pig serum on agar, and recently Bordet has further shown that this is the case even when the agar has been by special methods deprived entirely of its nitrogenous components and represents simply a complex of carbohydrates. Agar-guinea-pig serum mixtures of this kind show an increase in total nonprotein nitrogen which would prove that the proteolytic action of the guinea-pig serum must have been active against its own proteins.

An interesting further development of this work has recently appeared in the experiments of Jobling and Peterson.[15] They showed that when bacteria are mixed with fresh active serum they adsorb the antienzymes normally present in blood. They have shown this experimentally and have proved that similar antienzyme removal can be accomplished by the addition of kaolin or agar, and by treatment with chloroform. Serums so treated become toxic, the actions of the poisons formed showing great similarity to that produced by Friedberger's anaphylatoxins. According to them, the poisons are formed because of the fact that antienzymes are adsorbed by the antigen, thus setting the normal ferments in the fresh serum free to act on their own serum protein.

It should be recalled that Friedemann, who was really the first one to show that the toxic substances could result from the interaction of fresh serum and sensitized antigens, although he succeeded only in doing this with red blood cells, suggested rather early that the success of such an experiment does not necessarily mean that the antigen furnishes the matrix entirely. He had studied the metabolism in anaphylactic poisoning and with Isaac has shown that the nitrogen output following reinjection in a sensitized animal is far in excess of that which could be derived solely from the injected antigen, and in this he has been confirmed by many other workers, notably by Vaughan.

It would seem to us that our present knowledge of this phase of anaphylactic investigation permits us only to conclude that wherever proteolytic changes take place these "proteotoxins" may be formed. That they can be produced from a protein antigen has been shown

14. Bordet: Compt. rend. Soc. de biol., 1913, lxxiv, 877.
15. Jobling and Peterson: Jour. Exper. Med., 1914, xix, No. 5.

beyond doubt by Vaughan and his collaborators for both formed and unformed antigens. Also this is evident from the experiments of many workers and has been confirmed in our own experience with poisons appearing during the autolysis of bacterial emulsions. On the other hand, it is also clear that the antigen need not represent the matrix which furnishes the poison, and that in the reactions as they are generally performed both in the test tube and in the animal body, it is more than likely that if an antigen participates at all in furnishing the substratum for the poison, this is probably less important than that furnished by the animal's own proteins. However, this does not weaken the importance of the knowledge that the antigen-antibody reaction in the presence of normal serum and certain antigens in the presence of normal serum alone, induce a reaction in the course of which such poisons are formed. And the fact that they can be produced experimentally in the peritoneal cavity of a living guinea-pig renders their participation in such reactions in the animal body a likely assumption.

Our own work[16] on these substances induces us to believe that proteotoxins so formed are identical with Bail's aggressins, a point to which we will later refer.

Granted that such a poison, call it "proteotoxin" or "anaphylatoxin" or "serotoxin," as Jobling and Peterson have called it, is formed, it is important of course to determine as closely as possible its nature. Apparently the poison is the same as far as we can determine by pharmacological action when produced by the chemical methods of Vaughan or by the biological methods of Friedberger and others. As obtained by Vaughan it is water-soluble with slightly acid reaction, is freely soluble in alcohol and mineral acids. It is not diffused readily and contains no carbohydrates. In its crude state it gives a biuret reaction, although this may mean simply that the poison has not been completely derived. The fact that the injection of Witte peptone into animals may give rise to symptoms very similar to anaphylaxis has been taken by many workers to signify that the anaphylactic intoxication is produced by a poison which is very similar to, or possibly identical with, the active constituents found in this peptone. After peptone injection in normal animals there is a lowering of blood pressure, a delay in the coagulation of blood and a development of subsequent tolerance, together with many clinical symptoms which emphasize this similarity. Biedl and Kraus, who have especially studied this condition in dogs, have felt emphatically that the anaphylactic poison is probably very similar to peptone. Recently Dale has suggested that B-imidezolylethylamin or histamin may be the active principle con-

16. Zinsser and Dwyer: Jour. Exper. Med., 1914, xx, No. 6.

cerned in anaphylactic shock. Intravenous injection of 0.5 mg. of this substance into large guinea-pigs results in typical respiratory difficulties, convulsions with death and distention of the lungs typical of anaphylactic shock. Treatment with atropin diminishes this action, just as Auer and Lewis found this to be the case in true anaphylaxis, and fall in blood pressure also occurs. It would seem then that substances representing cleavage products of native proteins of highly complex nature, the result of proteolytic cleavage not very far advanced, are probably concerned in the production of anaphylactic shock. The anaphylatoxins of Friedberger cannot of course be studied chemically by the methods to which Vaughan's poisons are amenable.

IV

A further problem which has arisen in connection with the conception of parenteral digestion is that which concerns the participation of complement or alexin in the cleavage process during which the anaphylactic noxious agent is liberated.

When bacteria or red blood cells are sensitized, that is, have been combined with their specific antibodies, we have believed that it is the complement, or active constituents of fresh blood, which then acts on this sensitized complex, either producing hemolysis in the case of sensitized red blood cells, or the bactericidal or bacteriolytic effect in the case of sensitized bacteria. It is also well known to you that this substance, which we call complement or alexin, but about the true nature of which we know nothing, is fixed or bound by dissolved proteins when they have combined, with or without the formation of precipitates by their antibodies. We have ourselves[17] shown that such fixation of complement by precipitates (formed when an antigen and its precipitin have united) is bound in exactly the same way as this occurs in the case of sensitized red blood cells; that it is not a nonspecific physical complement fixation such as that which occurs when complement is fixed by kaolin, yeast cells or other unsensitized emulsion. From this knowledge there has gradually grown the conception that the complement or alexin may be a necessary, active factor in the cleavage of the antigenic molecule. (This may or may not be so; we may say we think that we have no proof at present that the complement acts as a proteolytic enzyme; on the other hand it is more than likely that in some way it is connected with such cleavage processes.) At any rate, since we know that the anaphylactic reaction is the result of the union of an antigen with its antibody, and this together with our knowledge of complement fixation, naturally suggests that the complement may be directly concerned in the mechanism of anaphylaxis.

17. Zinsser: Jour. Exper. Med., 1912, xv, No. 5; 1913, xviii, 219.

The first method of approaching this problem naturally was the examination of animals with regard to quantitative changes in the complement contents of the blood during anaphylactic shock. It was found by Sleeswijk[18] that animals actively sensitized and reinjected showed a very definite diminution of complement. However, under such conditions the diminution was neither rapid nor very extreme, facts since confirmed by Friedberger and Hartoch,[19] who found the diminution very much greater in experiments with passive sensitization. In such cases there was a regular and considerable diminution, so that after shock four to eight times as much serum was necessary to produce the alexic effect as before shock. Friedberger even believed that there was a definite parallelism between the intensity of shock and the degree of complement diminution. The question immediately arises is the loss of complement, which we may now regard as a demonstrated fact, an incidental effect of shock or has it causal relationship to the development of shock? The latter seemed at first to be likely for a number of reasons. It was found, in the first place, that the addition of complement to the circulation of an animal during the anaphylactic experiment did not serve to prevent shock. Similar evidence seemed furnished by certain experiments on the complement of birds, by work of Loeffler[20] and by the observation of Hartoch,[21] that but slight shock could be produced in guinea-pigs suffering from trypanosomiasis in which, as is well known, complement is greatly reduced. Loeffler also attempted to support this point of view by sensitizing guinea-pigs and then reducing their complement by the injection of sensitized beef blood intraperitoneally. Such animals showed diminution of reaction when reinjected with the sensitized antigen. Loeffler's experiments are not conclusive, since the action of the sensitized blood cells in the peritoneum must surely have induced an intoxication not at all unlike that taking place in true anaphylaxis, and, as we have shown recently together with Dr. Dwyer, such intoxications are followed by nonspecific tolerance to the anaphylactic poison.

However, another method of approaching this problem was attempted by Friedberger in his well-known salt experiment. It had been shown by a number of workers, among whom we may mention especially Nolf[22] and Hektoen,[23] that complement is not bound by sensitized complexes in the presence of hypertonic salt solution. In fact, hypertonicity seems to inactivate complement, and indeed it is a method

18. Sleeswijk: Ztschr. f. Immunitätsforsch., 1909, ii.
19. Friedberger and Hartoch: Ztschr. f. Immunitätsforsch., 1909, iii.
20. Loeffler: Ztschr. f. Immunitätsforsch., 1910, viii.
21. Hartoch and Sirenskij: Ztschr. f. Immunitätsforsch., 1910, vii.
22. Nolf: Ann. de l'Inst. Pasteur, 1900, xiv.
23. Hektoen and Ruediger: Jour. Infect. Dis., 1904, i.

of many laboratories to preserve complement for considerable periods by adding hypertonic salt solution, in which condition it will last a considerable time and is easily reactivated on dilution to isotonicity with distilled water. Friedberger[24] injected concentrated salt solution into sensitized guinea-pigs just before reinjection. It is possible, as he found and as we have found since, to inject 0.3 c.c. or even more of saturated salt solution intravenously into guinea-pigs of about 200 grams weight without killing them. When sensitized guinea-pigs were injected in this way and immediately afterwards received a toxic antigen injection, shock was definitely diminished and death averted. This has been one of the strongest bulwarks of those who have believed in the participation of complement in serum anaphylaxis. And it was assumed that the mechanism of the salt experiment consisted in a prevention of complement action. Recently doubt has been thrown on this because Ritz[25] has shown that salt injection not only prevents anaphylactic shock but will prevent the toxic effects of Witte peptone and of the so-called "anaphylatoxins." Recently with Dr. Dwyer[26] we have carefully repeated this work and have found that when the dose is carefully adjusted there is no question about the fact that an immediately preceding injection of concentrated salt solution will prevent death or even symptoms in animals injected with proteotoxins. This tends very strongly to diminish the weight of Dr. Friedberger's interpretation of the salt experiment; it means either that the salt in diminishing anaphylactic shock does so by a mechanism not concerned with the prevention of complement, or else it signifies that the so-called proteotoxin itself is not a finished poison as it has been thought to be but must still be acted on by the active constituents of serum before it becomes active.

It is true, indeed, that heating serum to a temperature of 56 C. renders it impotent to lead to proteotoxin production when added to antigen in vitro and that this same inactivation destroys the complementary effect on sensitized red cells or bacteria. This, after all, does not prove identity of the substances carrying these activities, but merely establishes an interesting parallelism.

We must not forget that the substance of which we speak as "alexin" or "complement" is not very well understood. We know little of its nature. It has been successfully shown that globulin participation will divide it into two parts, that it will spontaneously reactivate to a slight degree after heat inactivation, that its activity is influenced by concentration, and that it can be inactivated by shaking. We are

24. Friedberger and Hartoch: Ztschr. f. Immunitätsforsch., 1909, iii.
25. Ritz, cited by Doerr: Footnote 29.
26. Zinsser and Dwyer: To be published.

aware of the fact that we are here, possibly, dealing not with a single substance, but with one of the effects of a complex serum constituent. As to its relation to anaphylaxis we can only say that the diminution of complement during anaphylaxis is perfectly definite. However, we cannot claim with certainty, in spite of the evidence so far advanced, that it plays an active part in the production of anaphylactic shock.

V

The fact that the hypersusceptible condition can be transferred from a treated to a perfectly normal animal with the blood serum of the former, was in itself one of the first strong arguments in favor of the antigen-antibody conception of anaphylaxis. And this point of view was still more clearly defined when Doerr and Russ[27] subsequently showed that the power of a serum to convey hypersusceptibility was directly proportionate to its contents of specific antibodies. A serum which was strongly precipitating for the antigen would passively sensitize in quantities far smaller than those necessary for the same purpose in the case of a weakly precipitating serum. The principle that anaphylaxis depended directly on the meeting of the antigen with its specific antibody has never been seriously questioned since this time. However, from the very beginning of experimentation on passive sensitization it has seemed unlikely that the acute reaction, as seen especially in guinea-pigs, could be attributed entirely to the meeting of these two elements in the blood stream. It was observed by Nicolle, Otto, Friedemann, Gay and Southard and by many others since then, that sharp reactions can be produced with regularity only when a distinct interval was allowed to elapse between the administration of the sensitizing serum and the injection of the antigen. When the two are injected together, mixed, or simultaneously, symptoms may be and usually are entirely absent, whereas severe and unfailing shock results when the antigen injection is deferred from twelve to twenty-four hours after that of the sensitizing serum. According to Doerr and Russ the interval may be shortened to four hours, but if lessened beyond this, the reaction may fail to appear, or if present at all is weak and indistinct.

This observation alone would tend to convince us that mere contact within the blood stream of antigen cannot account for the entire train of phenomena and suggests that the characteristic anaphylactic reaction takes place only after the injected antibody has become attached to the body cells in the same manner.

The idea in itself is not new. Wassermann had first suggested it in an attempt to explain the peculiar hypersusceptibility to toxin possessed

27. Doerr and Russ: Ztschr. f. Immunitätsforsch., 1909, iii.

by some of Behring's toxin-immunized animals. He assumed that in such animals the formation of antitoxins may indeed have been stimulated, but that much of it might still be attached to the generating cells themselves, thereby rendering these proportionately more vulnerable to the injected toxin.

Such a conception of "sessile receptors" was applied by Friedberger[28] to anaphylaxis in his first attempts to formulate an hypothesis. He assumed that at the first or sensitizing injection the production of antibodies (precipitins) was stimulated. These, however, were not produced in great quantity and were not discharged into the circulation, possibly owing to the small single dose given for sensitization. They were present at the end of the anaphylactic incubation time as sessile receptors or sessile antibodies (precipitins). On the second injection a reaction occurred between the injection antigen and these sessile precipitins and the cell was injured because the reaction occurred on its substance, a reaction which, it is suggested, might have been harmless had it taken place in the blood stream. In passive sensitization, conversely, no injury could result until considerable quantities of the antibody had become united to body cells in the course of several hours. That the antibody injected into passively sensitized animals indeed disappears from the circulation with relative speed, has been shown by Doerr and again recently by Weil.

Besredka's[8] early hypothesis, too, though incorrect in most of its premises, assumed the necessity of the intravention of the body cell in anaphylaxis—an opinion here again largely based on the observed interval in passive sensitization; and the same idea occurs at about this time in the work of Doerr and Russ, who likewise conceived the process as taking place directly on the body cell.

It is true as Doerr[29] has pointed out in a recent summary of anaphylaxis, that these early hypotheses were for a time relegated to the background, yielding the prominent central position to opinions which held that anaphylactic shock was the result of intravascular parenteral digestion. To some degree this is due to the fact that Vaughan's work on the toxic protein split products and Friedemann and Friedberger's experiments on the production of similar poisons by purely biological methods, seemed to offer for the time being a field of work promising logical solution of this difficult problem. At the same time there was much evidence in the published work of such investigators as Friedemann, Scott, Briot, Biedl and Kraus, and Doerr himself which seemed to show clearly that the interval in passive sensitization was not an

28. Friedberger: Ztschr. f. Immunitätsforsch., 1909, ii.
29. Doerr: Ergebnisse der Immunitätsforschung, edited by Weichhardt, Berlin, 1914, i, 257.

invariable necessity. Consequently and very naturally the early purely cellular conceptions were not accepted as telling the whole story, and a few observers allowed the pendulum to swing completely away from this point of view. Nevertheless it is not fair to say that during this time the cellular theories were entirely neglected. We do not believe that von Pirquet ever entirely abandoned his original opinion that there was involved in certain phases of anaphylaxis an "allergie" of the tissues. Moreover, it was during this period that those methods of research were first applied to anaphylaxis which furnished in principle and fact all the important premises for the present almost universal cellular point of view. I refer to the transfusion method as employed in anaphylactic dogs by Pearce and Eisenbrey[30] and the method of observing isolated tissues from anaphylactic animals as used by Schultz[31]—work which appeared as early as 1910. Pearce and Eisenbrey working with two normal and one sensitized dog, transfused the blood of one of the normal animals into the sensitized one, transferring the blood of the latter to the normal dog. "At the proper moment the normal dog containing the blood of the sensitized animal and the latter containing the blood of the normal dog, each received intravenously the toxic dose of horse serum." The normal dog having the sensitized blood did not react, the sensitized dog having the normal blood showed typical fall of blood pressure. Pearce and Eisenbrey drew the conclusion "that the phenomenon of anaphylaxis is due to a reaction in the fixed cells and not either primarily or secondarily in the blood."

In the same year Schultz began to work with what is now spoken of as the physiological method. He determined that smooth muscle—freshly excised from various animals—will react with contraction when brought into contact with serum. When such muscle was taken from anaphylactic animals after being thoroughly washed free of blood, it would react more energetically and to smaller amounts of the homologous serum. There are many interesting by-products of Schultz's work, such as the differences between fresh arterial blood and blood serum in their abilities to stimulate contraction, but this and other points will not be discussed at present. The important and incontrovertible fact established by Schultz is the changed reaction-energy or, in truth, "allergie" of the smooth muscle of anaphylactic animals to the stimulus of the sensitizing antigen. Dale[32] has confirmed and extended these observations of Schultz. He removed the uteri from guinea-pigs after thoroughly perfusing them with Ringer's solution to remove all

30. Pearce and Eisenbrey: Congr. Am. Phys. and Surg., 1910, viii.
31. Schultz: Jour. Pharmacol. and Exper. Therap., 1910, i.
32. Dale: Jour. Pharmacol. and Exper. Therap., 1913, iv.

blood. He then suspended them in baths of Ringer's solution and by the customary physiological methods measured the contractions following the addition of various amounts of foreign protein in the form of —among other things—horse serum and beef serum. He found that the uterus of an animal sensitized to horse serum would react to this substance in dilutions of 1:2,000 or 1:10,000, while the organ taken from a normal guinea-pig reached its limit of reaction-ability at dilutions often less than 1:200. A uterus that had reacted strongly was found to be subsequently desensitized. A normal uterus could not—strangely—be passively sensitized by immersion into a solution containing serum antibodies. This method of investigation has recently, also, been taken up by Richard Weil[33] who has fully confirmed the principles laid down by Schultz and Dale. He has incidentally also answered an objection to the conclusions of Dale and Schultz (never indeed a very valid objection), namely, that the reaction of the muscle tissue of a sensitized animal might be in part due to the fact that the blood, i.e., the antibodies, had not been entirely washed out of the tissue spaces by perfusion. Weil performed the very simple and ingenious experiment of injecting a normal guinea-pig with large amounts of immune serum (anti-horse serum) and after a few minutes killing the animal. He then suspended the uterus in Ringer's solution in the usual manner without washing it completely free of blood. Contact with the homologous antigen produced no response. We may accept as definitely established by these researches of Schultz, Dale and Weil that the fixed cells of anaphylactic animals possess an increased reaction-ability toward the antigen which is in no sense secondary to processes involving the circulating antibodies. Moreover, the work of Weil seems to indicate that desensitization of a passively prepared guinea-pig deprives the uterus of its power to respond and that the gradual spontaneous diminution of hypersusceptibility on the part of the guinea-pig is accompanied by an entirely parallel loss of reaction-capacity on the part of the isolated uterus.

The recent work of Coca,[34] too, has further fortified the cellular point of view by a method which in principle is similar to that employed by Pearce and Eisenbrey. Coca succeeded in perfusing actively and passively sensitized guinea-pigs with the defibrinated blood of normal guinea-pigs in such a way that the original blood of the sensitized animals was reduced to a necessarily slight residue. Animals so treated could be kept alive for as long as six hours after the trans-

33. Weil, R.: Jour. Med. Research, 27, 1913; 30, 1914; Proc. Soc. Exper. Biol. and Med., 1914, xi, 86.

34. Coca: Ztschr. f. Immunitätsforsch., 1914, xx.

fusions and remained delicately hypersusceptible in spite of the blood substitution.

Limiting ourselves for the present to the phenomena of anaphylaxis in which noncellular antigens are employed, we may safely say that the evidence furnished by the incubation time necessary in passive anaphylaxis by the transfusion experiments of Pearce and Eisenbrey and of Coca, and most conclusively by the work on isolated tissue by Schultz, by Dale and by Weil, shows conclusively that the hypersusceptible state is largely determined by a changed reaction-capacity to the specific antigen on the part of the fixed tissue cells—an "alergie" which is probably due to the presence of specific antibodies in the substance of the cell protoplasm, and incidentally accounts for such effects as the skin reactions. It is probable that the acute symptoms and death of anaphylactic guinea-pigs (and indeed of other animals) is in most cases of experimental anaphylaxis due to the reaction which takes place between the injected antigen and these sessile receptors.

So much we must logically accept. However, are we justified in denying all possibility of injury to the animal when antigen and antibody meet in the circulation? This is indeed the claim of a number of workers who are inclined to regard the presence of circulating antibodies not only as incapable of leading to injury, but in fact as a protection, in that the antigen is deflected by them from the antibodies united with the cells. Personally we believe that this radical cellular interpretation of all phases of the phenomena of anaphylaxis goes too far. It was shown by Friedemann as early as 1909 that typical anaphylactic reactions could be produced in rabbits when the antigen (beef serum) was injected simultaneously with or mixed with the serum of passively sensitized rabbits. Indeed Friedemann claimed that by this method severe and fatal reactions could be produced in rabbits more regularly than when an interval was observed. Richet in the same year reported experiments in which immediate symptoms were elicited in dogs injected with mixtures of crepitin and the serum of a crepitin-treated dog, the crepitin in quantities far below that necessary to elicit symptoms in itself. (In this experiment of Richet the crepitin and the serum were left in contact in vitro for 20 minutes, a fact which somewhat detracts from the direct bearing of this work on our present discussion.)

In 1910 Biedl and Kraus[35] obtained immediate and severe symptoms in guinea-pigs when they injected intravenously mixtures of horse serum together with the serum of sensitized guinea-pigs. Briot[36] in the same year obtained reactions in young rabbits into which he had

35. Biedl and Kraus: Ztschr. f. Immunitätsforsch., 1910, iv.
36. Briot: Compt. rend. Soc. de biol., 1910, lxviii, 402.

injected mixtures of horse serum and anti-horse serum. Gurd[37] in a recent publication obtained reactions in guinea-pigs when he injected intravenously immune rabbit serum (anti-sheep serum) and immediately thereafter sheep serum. We ourselves have been able to obtain occasional and distinct results in rabbits and guinea-pigs both by simultaneous and immediately consecutive intravenous injections of antigen and antibody, though we did not succeed in attempts to duplicate exactly the experiments of Friedemann and of Biedl and Kraus.

We have here a not inconsiderable mass of evidence which points to the conclusion that the whole story of the anaphylactic phenomena cannot be told by the cellular conception alone, and that probably—as in immunity—both cellular and intravascular processes are involved. Few thoughtful workers on hypersusceptibility would think of denying at present the probably predominating cellular factor in the ordinary anaphylactic type-experiment. I may say that many of us have never doubted that this element was an undeniably important one in serum anaphylaxis since the time when the experiments of Pearce and Eisenbrey and those of Schultz confirmed the suggestion of this conception forced on us by the incubation time in passive sensitization and the studies of von Pirquet. We do not share, however, the exclusively cellular view recently advocated in a recent summary and apparently accepted by Doerr, one of the most capable students of this subject.

It is true that almost all of the workers cited above as having obtained passive sensitization, without the interval, admit the irregularity of such results, and Friedemann, Gurd and others call particular attention to the great importance of the relative amounts of antigen and antibody when these are injected together or in rapid sequence. This has been our own experience and although we have obtained very definite reactions in this way, we feel that in any given experiment success or failure cannot be as regularly foretold as in the experiments in which the interval is allowed. Moreover, the reactions obtained by these methods are often mild—delayed—and are rarely violent or rapidly fatal. We ourselves have never obtained a fatal result. Yet it is idle to say—as has been said—that the reactions so obtained are accidents, probably due to secondary factors, neglible in formulating a conception of anaphylaxis. There is no such thing as an accident in nature, and the observation, though irregular and depending on elements in the experimental procedures not easily amenable to control, has been made too often and independently by a number of different trained observers to be thrown out of consideration in a theoretical scheme which is to be just to all the facts.

37. Gurd: Jour. Med. Research, 1914, xxxi, 205.

Since we cannot, therefore, deny that under certain circumstances injury to the animal may result from the meeting of the antigen and antibody within the circulation, how are we going to account for the fact that such reactions are difficult to obtain and cannot be obtained with regularity? This question is not a simple one but it is our own opinion that a possible explanation may be found in the failure of rapid union of antigen and antibody in the blood stream. We have already mentioned that all observers who have experimented along these lines have found that very definite proportions between antigen and antibody govern the success of such attempts and that with each lot of serum and anti-serum the optimum proportions must be determined by experiment. In Friedemann's work on rabbits he found that the relative amounts of antigen and antibody which produce reactions in his rabbits if injected together corresponded roughly to the proportions which in vitro gave precipitates. An excess of one or the other substance would prevent reaction or at least result in a negative experiment. Now it is well known to all who have worked with antiprotein serums that the precipitin reaction can be inhibited by an excess of one or the other reagent.

When a constant amount of precipitating serum is used, the most prompt and voluminous precipitation may, for instance, occur when the antigen dilution is 1 : 50, and both the speed and the amount of precipitate may diminish not only as this dilution is increased, but also as the concentration is increased. This is a phenomenon which is common to all colloidal reactions and the mutual precipitation of the two colloids is to a large extent dependent on relative proportions.

It is a well-known fact (also familiar to many of you) that Linossier and Lemoine,[38] Eisenberg,[39] Ascoli,[40] von Dungern[41] and others have frequently noticed that animals treated with a foreign protein such as horse serum, for instance, may contain in their blood serum, as late as six, seven, eight or more days after injection, both the antigen and its antibody ununited and separated. Thus we have often seen ourselves, if we bleed an animal that has been rapidly treated with such a foreign protein, that its serum will precipitate horse serum, and will at the same time be precipitated by anti-horse serum taken from another rabbit. It is thus plain that the serum in the case mentioned contains not only horse serum as such (a remnant of that injected) but also antibodies against horse serum which have been formed in response to the injection. It is unquestionable from the experiments of others and from our own extensive confirmation, that

38. Linossier and Lemoine: Compt. rend. Soc. de biol., 1902, liv, 85.
39. Eisenberg, P.: Centralbl. f. Bakteriol., 1903, Orig., xxxiv, Part 1, p. 259.
40. Ascoli, M.: München. med. Wchnschr., 1902, xlix, 1409.
41. V. Dungern: Centralbl. f. Bakteriol., 1903, Orig., xxxiv, Part 1, p. 355.

the serum of such an animal may contain side by side free antigen and free antibody. Why have these failed to unite? If such a serum is allowed to stand at room temperature or in the ice box there will take place a very slow precipitation and a concomitant diminution in the amount of precipitin present. The precipitate thus formed has slight and distinct complement-fixing properties. Slow union, therefore, is taking place.

Another strange fact about such serums is that if two such rabbits are prepared, in each of which both free antigen and antibody can be determined, these serums when mixed will promptly precipitate each other.

A number of explanations have been advanced for the simultaneous presence of antigen and antibody in the same serum without union. Eisenberg and Volk have attempted to explain it by dissociation—that is the antigen and antibody are present united and also dissociated, reacting according to the laws of mass action. This has seemed to us unlikely. For, were this the case, the serum, as taken, should in itself exert definite complement-binding properties, since on the basis of this explanation it must contain not only the two reagents separate but a rather large proportion of the antigen-antibody complex united. This is not the case according to our own observations and according to similar ones made by Gay and Rusk.

Von Dungern[42] has assumed that the state of affairs described was due to the fact that the antigen might contain a number of different substances, alpha, beta, etc., each of which produces its own specific *Teil-präzipitin*. He believes it possible that at certain stages in the immunization the free antigen present might be, say, an alpha fraction, the free antibody, let us say, a beta precipitin, the two not fitting and therefore unable to react.

Auch hier handelt es sich nicht um zwei reaktionsfähige Körper, deren Verbindung aus irgend Grunden unterbleibt, sondern um Substanzen, welche keiner Affinität zueinander besitzen. Die betreffenden Kaninchen haben zu dieser Zeit noch nicht alle möglichen Teilpräzipitine gebildet, sondern nur einzelner derselben. Diese zunächst produzierten, nur auf bestimmte Gruppen der präzipitablen Eiweisskörper passenden Partialpräzipitine sind es, welche nach der Absättigung aller zur Verfügung stehenden zugehörigen Gruppen der präzipitablen Substanz im serum nachweissbar werden. Daneben bleit aber ein anderer Teil der präzipitablen Substanz, der keiner Affinität zu dem gebildeten Präzipitin besitzt, bestehen, solange bis ein anderes Partialpräzipitine von den Kaninchenzellen geliefert wird welches sich mit Gruppen der in Lösung gebliebenen Eiweisskörper vereinigen kann.

This has not seemed likely to us although they are clear when taken and remain so for considerable periods, but do eventually precipitate

42. Von Dungern: Centralbl. f. Bacteriol., 1903, xxxiv, first part orig.

slowly and in the course of days, an observation made not only by us but by Merckel.

It has seemed to us most likely that there might be in the circulation of animals an inhibiting agent, somewhat in the nature of a protective colloid, which prevented the union of antigen and antibody, or at least tended to make it an extremely slow process.

We may assume in the light of our present knowledge that both the antigen and the antibody are colloidal in nature, and together with Stuart W. Young,[43] we have been able to produce an analogy to the condition found in the serums just described by using three colloidal suspensions, that is, arsenic trisulphid, gelatin and gum arabic. Emulsions of gelatin flocculate suspensions of arsenic trisulphid; if small amounts of gum arabic are added flocculation is prevented. In order that a protected suspension shall be produced in which no precipitation will occur, very definite proportions between the three suspensions must be arrived at, but a number of quantitatively varying mixtures of the three can be produced which will hold up without precipitating for a considerable period. Like the serums described above, two such suspensions in which the relative proportions of the three are not the same will precipitate each other when by rapid mixing the quantitative relationship necessary for protection is suddenly disturbed.

We have here, then, a complex analogy to the conditions in the serums. Two substances, mutually flocculable, do not precipitate. They are prevented from precipitating by the presence of a third substance which "protects" when certain definite proportions between the three are maintained. Many quantitatively different mixtures of this kind may be made in which flocculation is in this way prevented. Mix two such protected mixtures, disturb these proportions and flocculation occurs, faster or slower according to the relations arrived at in the mixtures.

Moreover Porges[44] has shown that the factor of colloidal protection may well play a part in the occurrences taking place in a medium of blood plasma or serum. He has found that fresh native serum will precipitate mastic emulsions. The same serum heated, if used in very small quantities, will protect mastic emulsions against precipitation of the fresh serum. This alone shows what delicate physical changes in the body fluids may make for fundamental changes of reactions.

In our own experience these experiments of Porges were in principle confirmed; small quantities of heated dog serum added to arsenic

43. Zinsser and Young: On the Possible Importance of Colloidal Protection in Certain Phases of the Precipitin Reaction, Jour. Exper. Med., 1913, xvii, 396.

44. Porges, O.: In Kraus and Levaditi: Handb. d. Technik u. Methodik der Imm., Jena, 1909, ii, 1146.

trisulphid precipitated this suspension; slightly greater quantities again dispersed it. Of similar significance are experiments by Streng on the so-called conglutinins, substances in serum which are supposed to produce an agglutination of blood corpuscles or bacteria which have been previously treated with fresh serum or alexin. The addition of minute quantities of alexin to typhoid bacilli and agglutinin prevents agglutination.

Friedemann,[45] furthermore, a pioneer in this branch of serum investigation, in studies on the serum reactions has come to the conclusion that certain anticomplementary activities of the serum globulins may be inhibited by the albumins of the same serum. Schmidt[46] speaks of a similar *Schutzwirkung* on the albumin of normal serum. When lues serum was mixed with certain lipoid extracts (of human heart, used for Wassermann antigen) precipitation resulted. Such precipitation was brought about also by the globulins of normal serum—but was prevented or "protected against" when the albumin of normal serum was added to the mixtures. Friedemann himself (and Schmidt agrees with him on the main points) thinks that the globulins and albumins of normal serum are in antagonism, the albumins preventing certain reactions (such as complement fixation) in which the former become active as soon as the albumins are removed or diminished.

We do not have to force analogy to look on such serum reactions as essentially following laws similar to those observed in the case of chemically definable colloids. Apart from the protein character of serum constituents, we know that serum reactions follow quantitative laws analogous to those observed in colloidal reactions (inhibition zones, etc.). We know the importance of the electrolytes in the phenomena, we know that the immune bodies like the colloids diffuse but slowly, and we know from the work of Landsteiner and Pauli[47] especially, that certain serum hemagglutinins will wander, like other colloidal substances, to one pole or the other when a direct electric current is passing through solutions containing them, like amphoteric substances changing the direction of wandering according to the alkalinity or acidity of the menstruum. The points of similarity are too numerous to be exhaustively reviewed in this connection. They are so many and so striking, however, that we should hesitate to apply any explanation to serum phenomena of any kind which is not in accord with the general behavior of colloids.

In recent experiments of our own, moreover, we have been able to show that when precipitin reactions are set up in comparative series,

45. Friedemann: Ztschr. f. Hyg., 1910, lxvii.
46. Schmidt: Ztschr. f. Hyg., 1911, lxix.
47. Landsteiner and Pauli: Cited from Landsteiner, "Colloide u. Lippoide in der Immunität," from Kolle and Wassermann, Ed. 2, ii, 1244.

in one case using the globulins of normal rabbit serum, in salt solution, as the diluent for the antigen, and in another series the albumins of the same serum, the reactions in the latter are noticeably slower than in the former—than similar reactions in salt solution or in active or inactive serum. There is apparent inhibition of the reaction by the serum-albumin.

Enough has been said to show the justification of any theory which utilizes as a major premise the possibility of the participation of protective colloids in reactions taking place within the vessels of an animal. We suggested some years ago in a paper on this subject that it was such a protective colloidal action in the plasma of animals which prevented the rapid union of antigen and antibody in the blood stream, and we thought at the time that such an arrangement would indeed constitute an automatic protection of animals against sudden and severe injury when a foreign protein gained entrance to the blood stream. Our conception of the whole process would therefore be something as follows: The injection of a foreign antigen into the animal body leads it to antibody formation by the tissue cells. These antibodies are in part discharged in the blood stream and in part sessile on the cells. There is a gradual union between the circulating antigen and antibody and probably between the circulating antigen and the sessile antibodies. Under conditions apt to occur in the course of normal conditions the quantity of antigen which gains entrance is small and no injury results from such union by which probably a gradual parenteral digestion of the foreign substances is obtained. When in the course of abnormal states, infectious disease, etc., a situation arises in which considerable amounts of antibody have been formed and relatively large amounts of antigen are also present, all the conditions are furnished for what we call anaphylactic injury, unless there were some efforts to prevent the rapid union in these antibodies. In the anaphylactic experiment we see that the rapid union of antigen and antibody on the cell will kill. But it is likely that in most cases during immunization the circulating antibodies are far in excess of those still sessile on the cells, and were rapid union between these and the antigen not inhibited in the circulation, the animal would be constantly and severely ill during all processes of immunization. However, we know that in highly immunized animals antigen and antibody may be present side by side ununited. Is it not necessary to assume that this is evidence of a protective inhibition of union? For the colloidal protection would lead to a very slow union, in which, because of the gradual nature of the process, practically no severe injury of the individual could result. According to this conception we can quite easily explain why the simultaneous injection of antigen and antibody into the normal animal

would result ordinarily in slight and delayed symptoms. Accidental success in so balancing the proportions that complete elimination of protection results would account for the occasional acute symptoms and death observed in such procedures. It is quite clear that such an ideal experiment cannot be regularly obtained, for the simple reason that the protective element may be subject to variation, and since there are so many secondary factors even in test tube experiments on precipitation which influence such reactions.

When the animal is sensitized by the methods of the classical anaphylactic experiment, the union in the cells, violent and stormy, results in death after anaphylactic shock, and whatever symptoms might have resulted from the union of the two substances in the blood serum are overshadowed and secondary.

It is perfectly clear that there are many gaps in the absolute experimental proof of such a conception. We know, however, that slow, gradual and acute injury may follow on the simultaneous interaction of antigen and antibody in the animal body. We know from the many experiments of Vaughan, Friedberger and of others that in vitro such a meeting in the presence of active serum can result in the production of injurious substances which produce anaphylaxis-like symptoms when injected into the animal. We know from the experiments of Doerr that the injection of formed precipitates will injure. Whatever we may think about the nature of the poison and its mechanism of production there is little reason to doubt that the noxious agent can be produced without reference to the body cells. And we believe from this, together with the premises on which we have developed our idea of colloidal protection, that such a conception may form a perfectly legitimate explanation for the scattered and yet definite observations made since Friedemann, by many others and by ourselves, of immediate symptoms after simultaneous injection of antigen and antibody.

VI

In discussing the probable localization of anaphylactic reactions in the preceding paragraphs, we limited ourselves entirely to the phenomena occurring when sensitization is carried out with noncellular substances such as blood serum, egg albumin, etc.

When the antigen employed is cellular, consisting of bacteria or red blood cells, we are confronted with a problem of considerably greater complexity. As morphologically compact structures these cells cannot enter into direct chemical relations with the fixed tissue cells until they have been either disintegrated or at least have given up constituents to solution in the blood plasma. In consequence we must assume two separate phases of all such reactions—one the occurrences within the

circulating blood in which the injected cells come in contact with the solvent elements of the plasma and during which the solution of antigenic constituents is brought about, the other the subsequent reactions entered into by these dissolved substances, either within the circulation or on the fixed tissue cells with their respective receptors or antibodies.

If therefore Doerr[29] and others (Denzer and Weil) claim that anaphylaxis with cellular antigens is entirely similar in principle to that produced with dissolved, unformed antigens, they may well be perfectly right in so far as the second phase of these phenomena is concerned. They found that guinea-pigs injected with hemolytic serums reacted to the injection of the blood cells when, as in passive serum anaphylaxis, a latent period or interval was allowed to elapse between the administration of the antibodies and that of the nitrogen. This means simply that they failed to obtain acute or marked symptoms (for quantitative reasons possibly) when the cells and antibodies met in the blood stream.

Analyzing the phenomena in this way it becomes clear that when we inject cellular material we are merely injecting an antigen—or more probably a group of antigens—enclosed in the morphological structures of the cell, and amenable to reaction only after liberation. After this has taken place, subsequent occurrences should in no important principle differ from those following on the injection of an unformed substance like serum, or we may say for the sake of clearness, a predissolved antigen; and all that we have said about such conditions in our preceding discussion should apply here.

Added to this, however, we have in the case of cellular antigens a process unnecessary when unformed antigens are injected, namely, the cytolytic or cytotoxic reaction which precedes the liberation of the cell-constituents, and in the course of which the formed elements are broken up. And we need only compare the slow autolytic disintegration of cells in sterile inactive serum or salt solution with the rapid changes occurring in active hemolytic or, in certain cases, in bacteriolytic serums, to be convinced that such disintegration is due to reaction with active serum constituents.

We may logically accept, then, that by injecting cells, we are for one thing injecting substances which will, in part, soon be liberated and which will call forth all the changes and enter into all the reactions which are associated with the injection of dissolved antigens. In addition to this, however, we are confronted with a further problem. Is there injury to the animal body, comparable in broad principles with anaphylaxis, during this intravascular reaction between whole cell and

cytolytic antibodies which precedes the liberation of the soluble constituents? Is there, in other words, a true "cell anaphylaxis"?

Since it is probable that the principles of cellular anaphylaxis are the same whatever the variety of cell employed, we may take red cell hypersusceptibility as a basis for discussion. It is a well-known fact, long recognized, that a serum which is capable of hemolyzing the red cells of any species is toxic when injected into an animal of this species. This is true not only of hemolytic serums but also of such normal serums which like, let us say, goat serum and rabbit cells, can hemolyze normally the red cells of another animal. Since occasionally the serum of an individual of one species can so act on the red cells of another individual of the same species, our surgeons call for careful investigation of receptor and donor before performing transfusion. The injection of such a serum intravenously may kill with symptoms not unlike anaphylactic shock. Here it is often difficult, as we shall see (or indeed it may be impossible), to determine, whether such death is truly anaphylactic in nature or whether it is due to clumping of red cells or hemagglutination, a property which is very often an accompaniment of hemolytic power. However, hemagglutinating properties cannot be held responsible for the edema and localized injury which, as Uhlenhuth and Haendel have shown, may follow the subcutaneous injection of such serums. It thus appears as though the process of hemolysis were accompanied by the liberation of injurious products.

The first systematic investigation of red cell anaphylaxis was undertaken by Ulrich Friedemann.[11] Friedemann injected washed beef cells into rabbits and followed this by a second injection after from seven days to three weeks. Rabbits so treated showed the symptoms ordinarily associated with anaphylaxis in these animals. Active sensitization seems thus to have been accomplished with beef cells. Schiff and Moore have recently suggested that Friedemann really obtained serum anaphylaxis, but since Friedemann explicitly states that he worked with washed cells, we can see no just reason for such an assumption. Another objection to Friedemann's results, however, is possible—one which is far less easy to controvert—namely, that the illness of his rabbits may have been due to hemagglutination, which by itself may produce serious illness or even death by mechanical obstruction of blood vessels. Friedemann, indeed, takes cognizance of this possibility but makes no attempts to rule it out in his experiments. As a matter of fact we think it unlikely that hemagglutination played a part in his rabbits, but the possibility cannot be excluded. We will revert to this particular question.

Passive sensitization was produced by Friedemann against beef cells in rabbits by injecting the specific hemolytic serum. He obtained

his best results when he injected serum and cells together, mixed in vitro. However, he also obtained positive experiments when the two were simultaneously injected into opposite veins. His results were inconstant when he allowed an interval to elapse between serum and cell injection—a fact which argued for the direct occurrence of the reaction within the circulation.

Most important of all, Friedemann mixed hemolytic serum and cells in test tubes, letting them stand for five minutes in a water bath and then, before any considerable degree of hemolysis had taken place, he centrifugalized and injected the faintly red supernatant fluid into rabbits. A rabbit so injected became extremely ill and many of them died after shorter or longer intervals, with symptoms typical of anaphylaxis in rabbits. Friedemann concluded that when red cells came in contact with hemolytic antiserum, poisonous substances were liberated, even before actual hemolysis had taken place, and that these toxic products were responsible for the subsequent injury to the animal. He identified the anaphylactic antibody with the hemolysin. This view, therefore, is identical in principle with the one we have discussed as the conception of parenteral digestion. Indeed Friedemann's experiments furnished the point of departure for Friedberger's subsequent work on the so-called "anaphylatoxins."

Doerr and Moldovan,[48] a little later (1910), studied the effects of the injection of serums hemolytic for guinea-pig erythrocytes into guinea-pigs, and drew conclusions which substantiated those of Friedemann. They found that the toxic effect was due to the action of the hemolytic serums on the guinea-pig erythrocytes. Toxicity could be removed from such serums by absorption with these cells, and the toxic products could be produced by contact of serum and cells in vitro. From these experiments, again, it seemed that the liberation of a toxic substance followed on contact between erythrocytes and specific antibodies, whether this contact took place within the circulation or in the test tube. That the antibodies concerned need not necessarily be identical with hemolysins themselves follows, we think, from the work of Doerr and Moldovan as well as from work of our own on the toxicity of certain normal serums[49]—experiments which could not be discussed in detail without taking more space than seems justified.

Although much irregularity of result has been obtained in the production of active erythrocyte anaphylaxis in both guinea-pig and rabbit experiments, nevertheless, it seems clearly established that acute death does follow the repeated injection of such cells when dosage and interval are properly observed. The recent experiments of Schiff and

48. Doerr and Moldovan: Ztschr. f. Immunitätsforsch., 1910, vii.
49. Zinsser: Jour. Exper. Med., 1911, xiv, No. 1.

Moore,[50] though they clearly illustrate the difficulties of such procedure in guinea-pigs, still record a sufficient number of positive results to reconfirm its actual occurrence. From one of these experiments, indeed, as well as from the experience of Friedemann and others with passive sensitization by antierythrocyte serums, it would appear that with red cells the phenomenon requires a procedure differing from that successful with serum anaphylaxis, in that a considerable concentration of antibodies is needed, i.e., a condition calling in the active experiment for more than one preparatory injection, or, in the passive sensitization, for the injection of a serum of high potency. This, as we know, is the case, also, in bacterial anaphylaxis, in which experiments are usually successful only if many and repeated preparatory injections are made. It is this factor, possibly, which may account for the failure of so many workers to obtain true cell anaphylaxis when they have followed the technic successful in the serum experiments—i.e., that of only one preliminary sensitizing dose—or that, in the passive experiment, many have failed to duplicate Friedemann's success when both antigen and sensitizer were simultaneously injected. It is more than likely that a weak sensitization and consequently a slow reaction between the cells and the antiserum may be interrupted by prompt phagocytosis of the injected cells, with consequent protection against the further developments of the process.

It is true that in many cases of erythrocyte anaphylaxis it may be impossible to say with certainty whether death was due to true shock or whether it was caused by embolic processes due to hemagglutination. This possibility has not been ruled out in many otherwise complete investigations—though in experiments like those of Friedemann and Amako[51] it seems but a remote possibility. However, in individual instances, such as our own experiments with normally toxic serum, it has been shown that the toxicity may disappear with inactivation, though hemagglutinating properties are retained, and it seems that, to kill acutely hemagglutination must be rapid, powerful and extensive. Moreover, the speed and completeness of recovery showing non-lethal degrees of erythrocyte anaphylaxis argues at least against the frequent occurrence of hemagglutinative death by embolism in experiments carried out in this way. The local injury following the subcutaneous injections of normal and immune hemolytic serums must of course occur entirely independent of hemagglutination. Finally, the fact that contact of the cells with active serum—as first carried out by Friedemann—produces a poison in vitro which kills acutely with symptoms of anaphylaxis, seems to render fairly certain the assumption that

50. Schiff and Moore: Ztschr. f. Immunitätsforsch., 1914, xxii.
51. Amako: Ztschr. f. Immunitätsforsch., 1914, xxii.

similar contact in the circulation may lead to like result. For we know that the entire process of hemolysis can take place intravascularly.

Whether the antibodies that so react with the cells are the hemolysins themselves, is a question that we hardly have the time to discuss and which moreover is merely an incidental one. After all, hemolysis itself is merely one visible result of a reaction which probably affects profoundly the entire cell structure. About bacterial anaphylaxis our knowledge is still more defective than is that occurring when erythrocytes are used. We *do* know, however, that active sensitization with bacterial proteins and with whole bacteria is possible—though many injections are apparently necessary—the exact procedure being subject to so many fortuitous influences that so far no regularly successful method can be outlined. We also know that, as with red cells, contact between the bacteria and active serums will result in the production of acutely toxic substances—which we have discussed above as "proteotoxins."

SUMMARY

We may summarize our views on cell anaphylaxis, briefly, as follows: When whole cells are injected into an animal two distinct processes are set in motion. First, the formed cells come into relation with circulating antibodies. During this contact toxic substances—"proteotoxins"—may be set free if quantitative relations are suitable and cells sufficiently sensitized. Where the matrix of the poison is found and to what an extent the complement participates—these are in many respects still open questions. This reaction alone, if sufficiently vigorous, may cause acute symptoms and even death.

During this reaction antigenic cell constituents are set free to solution and these then enter into reaction with their respective antibodies or receptors in the blood or on the fixed cells. The last-named reactions are entirely comparable to those of serum anaphylaxis and have been sufficiently discussed.

Whether in the first-named process, when the whole cell meets its antibody in the blood stream, we regard the poison as originating from the matrix of the antigen or from the serum itself by the withdrawal of antienzymes is immaterial. The reaction is subject to so many modifying factors that experimental control is made difficult and results cannot at present be so regularly foretold as is the case in serum anaphylaxis. It seems probable from the work of Friedberger and others that a delicately balanced optimum proportion between antigenic cells and antibodies must be obtained. Moreover, unless the process is rapid and harmful effects very sudden, prompt phagocytosis of the cellular elements may remove the antigen from further reaction possibility.

It is plain that such a conception has the greatest importance in the understanding of infectious diseases. When bacteria form the antigen which gains entrance to the animal body, the gradual stimulation of specific antibodies in the animal may eventually lead to such a two-phase reaction. Specific sensitizers or amboceptors (cytotoxins) are gradually formed and these may react with the dead and the living micro-organisms. There may be a direct formation of proteotoxins and at the same time a liberation of soluble antigen from the bacteria. It may be, as von Pirquet has suggested, that the sufficient establishment of such reactions between cell and antibody may mark the end of what we speak of as "incubation time," no noticeable time accruing to the animal body until the antigen-antibody reaction has been initiated. The "proteotoxins" so formed, whatever their matrix, may then, as we have shown with Dr. Dwyer, act as aggressins, lead to a leukopenia, as in typhoid fever, and thereby increase indirectly the invasive capacity of the micro-organisms. The antigenic substances which have gone into solution may at the same time react both on the fixed cells with sessile receptors, and, to a merely incidental degree, with their receptive circulating antibodies, adding thereby to the injury sustained by the host.

True immunity against dissolved antigens, we have stated in the beginning, probably does not exist, for animals having high antibody contents in their serum may still die suddenly with convulsions after a fourth or fifth injection with foreign serum. In the case of cellular antigens, however, and especially bacteria, true immunity may exist in two forms. On the one hand if the animal possesses a high concentration of antibodies before the micro-organisms have gained entrance, an immediate bactericidal effect may prevent their multiplication, the harmful effects resulting from the union of the small initial amounts of antigen and antibody being so slight as to be unnoticeable. Again, after the bacteria have gained entrance, if the quantitative relations between antigen and antibody are such that the reaction is either slight or for purely quantitative reasons results in little injury for the time being, then sensitization of the bacteria or other cells by the antibodies, leads to rapid phagocytosis. And this process of phagocytosis represents true immunity, a removal of bacteria incidental to which there is, as far as we know, no injury to the host. It is in the process of phagocytic removal, chiefly, in which the reaction to cell injection differs from that taking place in response to the administration of unformed protein. It may be this element which renders it so difficult to obtain sharp anaphylactic reactions with cellular antigens. And it is the absence of phagocytosis in the latter case which probably prevents the existence of a true immunity.

AMAUROTIC IDIOCY *

GENERAL AND HISTORICAL CONSIDERATIONS WITH REPORT OF A CASE

JULIAN MAST WOLFSOHN, M.D.

PATHOLOGICAL REPORT BY JEAN R. OLIVER, M.D.
SAN FRANCISCO

Amaurotic familial idiocy—a clinical entity of which about one hundred cases are on record, is of great interest to the general medical profession because its symptoms are relatively so definite but rarely so correlated by the observer as to be recognized as the disease we are about to discuss.

The forerunners of the discovery of this disease were the ophthalmologists, chief of whom was Warren Tay,[1] who, in 1881, published an article under the caption "Symmetrical Changes in the Region of the Yellow Spot in Each Eye of an Infant." Tay found that in his patient, a child of 12 months, in the region of the macula, there was a large whitish patch, in the center of which was a brownish red spot similar to that caused by embolism of the central artery of the retina. He considered this change probably a local congenital disturbance. Later, in 1884, he reported[2] three more cases with the same condition in the same family, all of whom died at 2 years of age.

Three years later B. Sachs[3] made his noteworthy observations on the character of this disease in a paper on "Arrested Cerebral Development." In 1892 he reported a second case in the same family. Both children died at 2 years, had the same clinical symptoms and signs, and the brain of each showed the same pathologic changes. Sachs could give no explanation of the causes of this disease but said they were probably fetal-agenetic.

Carter[4] first recognized that the cases thus far corresponding to Sachs' were of Hebraic extraction and that "while to date, the majority of the cases reported belong to that race, by no means do all."

The term "amaurotic family idiocy" was proposed by Sachs in 1896, when the familial character of this disease was almost uniformly found. To this time 19 cases were described as having occurred in ten families. Combining the symptoms of all the cases

* Submitted for publication March 24, 1915.

1. Tay, Warren: Tr. Ophth. Soc. United Kingdom, 1881, i, 55.
2. Tay, Warren: Tr. Ophth. Soc. United Kingdom, 1884, iv.
3. Sachs, B.: Jour. Nerv. and Ment. Dis., 1887, xiv, 541.
4. Carter: Knapp's Arch. Ophth. and Otol., 1894, xxiii, 126.

then known Sachs was able to arrive at a definite symptom-complex which he says is pathognomonic:

1. Mental impairment in first few months of life leading to absolute idiocy.
2. Paresis or paralysis of the greater part of the body—flaccid or spastic in type.
3. Reflexes may be deficient or increased.
4. A diminution of the vision, terminating in absolute blindness (changes in the macula lutea and later an optic-nerve atrophy).
5. Marasmus and a fatal termination as a rule about the second year.
6. The occurrence of the affection in several members of the same family.
7. Healthy at birth, remaining so up to the third or fifth month; and occasionally —
8. Nystagmus.
9. Strabismus.
10. Hyperacuity of hearing.
11. Inordinate laughter was present in one case, and
12. Disturbances in deglutition were occasionally observed in others.

This syndrome then, as described by Sachs, is one made up of a number of symptoms most of which occur in many other organic nervous diseases, but chief stress up to this time was placed on its familial character, racial predisposition and the fact that it occurred shortly after birth.

It remained for Vogt[5] in 1905 to describe a condition in young children similar to that which Sachs described in infants. This author considered these juvenile cases a separate entity and he proposed the term "juvenile family amaurotic idiocy" for them. The findings in his patients were that the disease is familial in character, has no predilection to the Jewish race, begins in early youth, leads slowly to blindness, frequently to paralysis, and death occurs after several years.

Vogt had six cases (two in one family, one in the second and three in the third) in all of which the children were normal to the fourth to seventh year when there was gradual onset of blindness with optic-nerve atrophy (one case showed frequent deposits in the retina), dementia, paralysis and death from two to fifteen months later.

Vogt states that he believes Tay-Sachs' disease and the juvenile form of family amaurotic idiocy represent different degrees of the same process, but that Tay-Sachs' disease is so sharply characteristic that it may well retain its name.

Soon after this Batten[6] described two more cases of the juvenile type, one patient having "fits," together with dementia and retinal changes. His patients, like most of those cited above, died of marasmus.

5. Vogt: Monatschr. f. Psych. u. Neur., 1903, xviii, 163, 320.
6. Batten: Tr. Ophth. Soc. United Kingdom, 1903, xxiii, 386.

Mayon,[7] Higier,[8] Ichikawa,[9] Wandless,[10] Dercum,[11] Turner,[12] Gordon[13] and others have added materially to this list so that now there are probably about thirty cases of the juvenile type on record.

In a paper of this character a paraphrase of each case would be out of place, but a combination symptom-complex of the reported cases shows normal growth and development until 3 years or later, failing mentality and sight (with gradual optic-nerve atrophy and retinal changes), gradual onset of paralysis (flaccid or spastic), with or without convulsions; irritability of temperament, nystagmus, familial tendency without predilection to the Jewish race; death usually from marasmus.

Fig. 1.—Patient D. F., aged 7 months.

The following clinical and pathologic report of the author's case may serve further to emphasize the close relationship between the two types of amaurotic idiocy.

D. F., a girl, aged 6, entered the Children's Hospital because of "fits." Neither her parents nor any of her antecedents were of Hebraic extraction. Both parents are living and well and are not related. The daughter of a maternal uncle "had no control of her body at birth and died of brain trouble at between 4 and 6 months." A maternal granduncle died of "brain fever" at 14 years. There is no specific history in either parent. The Wassermann test in the mother's serum was negative. She had one miscarriage but no stillbirths. The patient was born at full term after a two-days' labor terminating with a hard, high forceps delivery. The child was fed with proprietary foods from the first and never nursed. Its mother claims that the infant was kept

7. Mayon: Tr. Ophth. Soc. United Kingdom, 1904, xxiv, 142.
8. Higier: Deutsch. Ztschr. f. Nervenheilk, ix, 1.
9. Ichikawa: Klin. Monatsbl. f. Augenheilk., 1909, xlvii, 73, 432.
10. Wandless: New York Med. Jour., 1909, lxxxix, 953.
11. Dercum: Jour. Nerv. and Ment. Dis., 1897, xxiv, 396.
12. Turner: Brit. Jour. Child. Dis., 1912, ix, 193.
13. Gordon: New York Med. Jour., 1907, lxxxv.

drunk with gin for the first month of life. She was a fat but not strong child. A severe attack of pertussis occurred in the second year, but subsided without complications. This was soon followed by "inflammation of the bowels" with high temperature, but recovery was complete.

From 2 to 2½ years the patient ran, played and talked — an active, healthy, apparently normal child. (See Figs. 1, 2 and 3.)

At 3 she had "black measles." This was followed by "food poisoning" after eating canned deviled ham. The patient nearly succumbed. About three months later she had an attack of "indigestion" accompanied by unconsciousness and stiffness of the whole body. Recovery ensued which was followed by the measles.

Just about this time (age 3½ years) the mother noticed that the child had a slight limp. A chiropractic physician was called who found the hip was "out" about one-half inch. This he replaced without benefit to the child.

The patient's eyes began to "wander with a bewildered look" and a few days later she awakened with "attacks of crying and trembling and rigidity of the arms and legs which lasted for a few minutes." These attacks increased in frequency, as many as twenty a day being noted. Sometimes one side alone, sometimes both sides, and at others the head or arms alone were convulsed.

Fig. 2.—Patient D. F., aged 9 months.

After some of these attacks the patient showed strabismus the rest of the day. A sudden noise or jar would bring on a "spasm."

Because of increasing rigidity, which became rather constant about six months after onset, the patient was unable to help or feed herself and could not walk. From a bright, healthy, active child within six to eight months she became a dull, apathetic, inactive invalid who gradually ceased to notice objects about her. (See Fig. 4.) The bowels were obstipated, necessitating daily enemas. Urination was involuntary.

Three years after the onset of the disease the patient presented the following positive findings:

A poorly nourished girl, only the purely vegetative functions persisted. Uncovering the patient or even clapping the hands in the vicinity of the bed, slamming the doors, etc., caused marked convulsive movements of the extremities and opisthotonus which lasted from ten to fifteen seconds.

There was a striking growth of hair on the extensor surfaces of the arms, legs and labia majora and the upper part of the back. The average length of these hairs measured three-fourths of an inch. The hair generally was thick and moist.

No scars or eruptions were present but the skin of the neck was deeply pigmented.

No cranial deformities were present.

Eyes: The child was blind. No spontaneous nystagmus or ocular palsies were noted. The left pupil was larger than the right; both reacted very sluggishly to light and measured from 4 to 5 mm.; bilateral optic atrophy was present and the retinal vessels were very narrow. In the region of each macula there was a grayish-white area in which was seen a small brownish-red spot. The retina, besides being very thin, showed no deposits or abnormal changes elsewhere. This finding was confirmed later by Dr. L. D. Green.

Ears: These showed marked hyperacuity of hearing. No visible pathologic changes were noted.

Mouth: The upper incisors were separated 3 mm. No anomalies of dentition were present. The palate was high arched. Frequent gnashing of teeth (trismus) occurred during examination.

Glands: The thyroid and thymus were small; the pectoral and posterior cervicals shotty, the inguinals large.

Chest: The lungs and heart were negative. The abdomen also was negative.

Fig. 3.—Patient D. F., aged 13 months.

Spine: With the patient in the sitting position the head fell forward, backward or laterally. The spine was very rigid on attempt at flexion or extension, but otherwise negative.

Extremities: Marked diplegia of spastic type was noted.

Upper extremities: Attitude — the fingers were flexed on the hands, the hands on the forearms. The forearms were flexed on the arms and everted. Attempts at pronation and supination were difficult. Passive movements were resisted but were not painful. The pectorals were tense. Placed in extension, the arms gradually assumed the position described above.

Lower extremities: Very spastic and held in forced extension with the feet in equinovarus position. The Kernig sign was positive. The vasomotor system showed acrocyanosis. There was a general bluish mottling of the skin.

Reflexes: These were everywhere much increased. Dorsal flexion of great toes occurred on plantar stimulation. No clonus was elicited. No signs of inherited syphilis were found. The patient expressed no communication with the outer world, could not feed herself, see or speak, but cried a good deal when handled.

Laboratory Tests: Blood: Red blood cells, 4,190,000; white blood cells, 8,500; Differential: Polymorphonuclears, 64 per cent.; small mononuclears, 28 per cent.; large mononuclears, 7 per cent; eosinophils, 1 per cent.

The Wassermann test was negative.

The urine had a specific gravity of 1.008, was acid and contained a trace of albumin. Fehling's was negative.

The microscopic examination was negative.

The cerebrospinal fluid under pressure of 120 mm. was clear.

The white cell count was 2 per cubic millimeter. The Nonne, Noguchi and Fehling's tests were negative.

The Wassermann test in the spinal fluid was negative. The temperature varied between 97 and 100.5. The pulse ranged from 90 to 100.

Fig. 4.—Patient D. F., aged 4 years.

Generalized convulsions occurred about every week and lasted from three to five minutes. Twitchings, or rather tonic spasms of the quadriceps femoris, all the muscles of the shoulder girdle, arms, hands, and neck, developed and were continuous except during sleep. The introduction of stovain (1/30 gr.) into the subarachnoid space controlled the spasms for six hours. Finally the spasms of the masseters became so severe that the lower jaw was dislocated. Meantime dysphagia and marasmus became very marked, the temperature rose suddenly to 105 and the patient died, three years after the onset of the disease.

The brain alone was permitted to be removed at necropsy, three hours after death, by Dr. J. Oliver, whose studies on the pathology of this case are detailed hereafter.

The chief interest now centers itself about the etiology of this disease, which still is a matter of much discussion. Is the disease inherited or due to some inherent defect in the gray matter of the central nervous system, or, if acquired, is it due to some kind of degeneration? Pathologic studies alone can help us in this search.

Sachs thought the disease was due to "an arrest of cerebral development"—agenesis corticalis, as he called it. Others, including Kingdon,[14] thought it an acquired disease, purely degenerative in character. Still others considered the changes due to certain toxins, syphilis or tuberculosis.

Sachs says: "A child to be afflicted with amaurotic family idiocy is born with a limited and restricted capacity for normal development. Its gray cells may do as well as any other child's up to 2, 3 or 6 months, but beyond that its powers for further development will not go." Therefore, he considers this disease a *congenital affair* in which, when normal development ceases, degeneration begins.

Hirsch[15] emphatically is determined that its character is acquired, caused by toxemia.

In the case cited above a family history pregnant with nervous disorders (some of which might have been similar to the disease under discussion), alcoholism soon after birth, and later food poisoning were prominent features. Could not this child have had a nervous system which was fertile soil for the production of this disease by disturbed metabolism with toxemia produced by alcohol and food poisoning? Dixon and Cohen[16] have tried to unite the inherited, toxic and degenerative theories advanced, and this case seems an ideal one, not only to justify a suitable explanation for its etiology, but to knit more closely the two types of this disease into one, namely, amaurotic family idiocy.

PATHOLOGIC REPORT

Few nervous diseases have received the careful study that has been given to the pathologic anatomy of amaurotic family idiocy. Though a comparatively rare disease, we know the structural changes which characterize the process so definitely that we may consider them pathognomonic of the disease. It is with some hesitation, therefore, that a detailed description of a new phase is given. Certain more unusual appearances have been met, however, which merit attention, and for the sake of completeness the entire findings have been given.

The literature of the subject has grown to such enormous proportions since the appearance of Sachs' original description[3] that a

14. Kingdon: Tr. Ophth. Soc. United Kingdom, 1892, xii.
15. Hirsch: Jour. Nerv. and Ment. Dis., 1898, xxv, p. 538.
16. Cohen and Dixon: Jour. Am. Med. Assn., 1907, xlviii, 1751.

review of the subject is impractical. Among the pathologic studies Schaffer's,[17] Vogt's,[18] Spielmeyer's[19] and Mott's[20] works are representative. We would, however, note the articles of Bielschowski,[21] Frey[22] and Schob,[23] who have paid particular attention to the changes in the cerebellum, as similar alterations were found in our case.

The necropsy was done by me two hours after death. The body was that of an extremely emaciated, fairly well-developed female child of apparently 7 years of age. There was a marked atrophy of the muscles of the extremities. The pupils were equal and dilated. No superficial enlargements of lymphatic glands were seen. The abdominal and thoracic cavities and their contents were negative, with the excep-

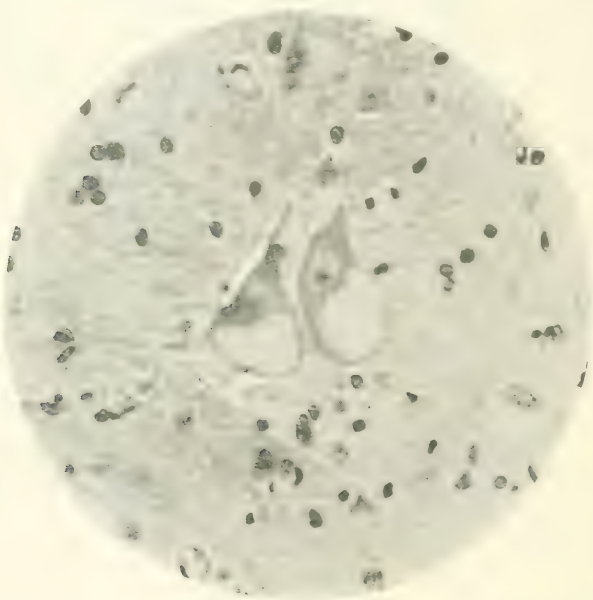


Fig. 5.—Precentral gyrus, Nissl stain. From photomicrograph. Two large pyramidal cells are seen with typical inflated areas. The nucleus of one is apparently normal. (Spencer 4 mm. Obj. Compens. Oc. 9x).

tion of a bronchopneumonia in the lower lobes of both lungs. The head was well shaped, and the skull of normal thickness and contour. The dura was somewhat loose, apparently normal, there being no remains of any old trauma from the difficult labor. The pia showed

17. Schaffer: Neurol. Centralbl., 1905, xxiv, 386, 437.
18. Vogt: Arch. f. Kinderheilk., 1909, li, 1.
19. Spielmeyer: Histol. v. Histopoth. Arbeit. (Nissl), ii.
20. Mott: Arch. Neurol., iii, 1907, 218.
21. Bielschowski: Deutsch. Ztschr. f. Nervenheilk., 1913, 1, 7.
22. Frey: Virchow's Arch. f. path. Anat., 1913, ccxiii, 308.
23. Schob: Ztschr. f. d. ges. Neurol. v. Psychiat., Orig., 1912, x, 303.

a diffuse thickening over the anterior portions of the cerebrum, and over the base of the brain. The convolutions of the cerebrum were normal in arrangement, showing none of the abnormalities described by previous authors, such as, a communication of the rolandic with the sylvian fissure, a gaping of the opercula to show the insula, or irregularities in the anterior calcarine fissure. The gyri in the frontal regions were distinctly narrower than normal, and there was a consequent widening of the otherwise normal sulci. The hypophysis and large venous sinuses at the base of the skull were normal. The brain was hardened in 10 per cent. formalin, and gross frontal sections made. In none of these was any abnormality in the white or gray matter noted.

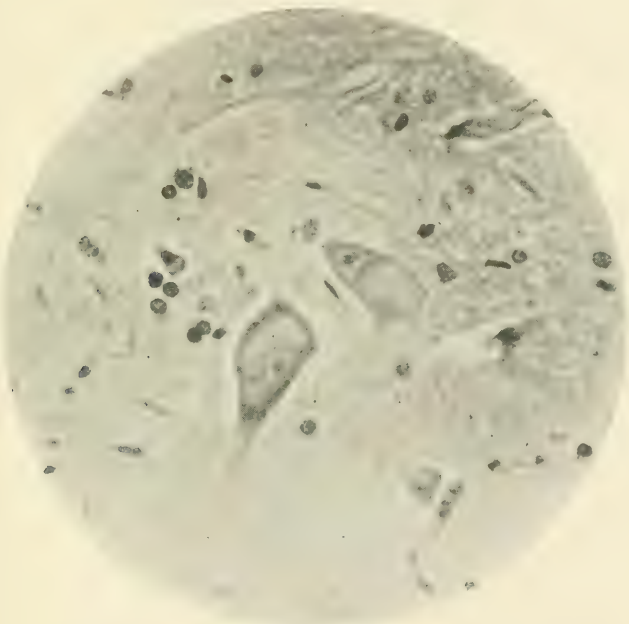


Fig. 6.—Anterior horn cells of cervical cord, Nissl stain. From photomicrograph. One cell shows the "inflated area" and in the other a small amount of the tigroid substance still persists in the neighborhood of the nucleus (Spencer 4 mm. Obj. Compens. Oc. 9x).

For microscopic study sections were prepared from various regions and stained with the Weigert-Pal, Nissl, Bielschowski and Mallory's phosphotungstic hematoxylin methods.

Ganglion Cells.—The ganglion cells of the central nervous system, whether motor or sensory, showed the same type of lesion. The changes were especially well marked in the precentral gyrus (Fig. 5), the Purkinje cells of the cerebellum, the cells of the dentate nucleus and the anterior motor cells of the cervical cord (Fig. 6).

The changes consist in a solution or disappearance of the Nissl substance with an accompanying distention of the cell body at this point, so that the term "inflated" has been applied to describe the appearance. The lighter staining degenerated area thus produced in the nerve cell is filled with a delicate reticulum. The nucleus is, as a rule, displaced to one extremity of the cell and often shows pyknosis, though it may retain an apparently normal structure (Fig. 6). The disappearance of the tigroid substance begins in the neighborhood of the nucleus and extends gradually to the periphery of the cell (Fig. 5).

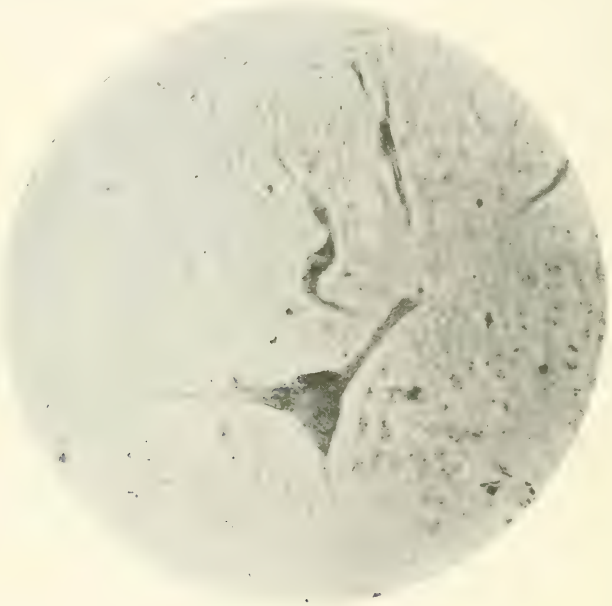


Fig. 7.—Purkinje cell of cerebellar cortex, Bielschowski silver impregnation. From photomicrograph. The upper part of the cell body is filled with deeply staining black granules. In the vertical dendrites are seen swollen areas filled with similar granules. (Spencer 4 mm. Obj. Compens. Oc. 9x).

The intracellular fibrils, as shown by the Bielschowski method, are entirely lacking in the "inflated" areas in the cell body, and persist only at the extreme periphery of the cell. The fibrillar structures of the dendrites and axons are as a rule normal.

The Sudan III preparations show the inflated areas of the affected cells to be filled with a fatty substance which stains a light orange-yellow. This lipoid material is very finely divided so as to give a ground-glass appearance rather than of separate droplets.

Somewhat different appearances are seen in the Purkinje cells of the cerebellum. Here the characteristic inflation of the cell body with

displacement of the nucleus is seen, but the process extends as well into the dendrites. On these structures are seen irregular swellings sometimes as large as the cell body itself. The contents of these protuberances are either clear and resemble the "inflated" areas in the cell body, in which case they may be shown to contain a fatty material, or they are filled with densely packed, silver-reducing granules (Fig. 7). Similar silver-reducing granules are seen in the cell bodies proper, and it would seem probable that they are of lipoidal nature. The axons, as far as they could be followed in the sections, were entirely normal.

The above described changes in the ganglion cells occurred with striking regularity throughout the entire central nervous system. There was, however, no marked decrease in the number of ganglion cells either in the cortex cerebri, in the Purkinje cells of the cerebellum or in the nucleoli of the brain stem. The arrangement of the layers of the cortex cerebri was still apparent, though somewhat indefinite on account of the marked degeneration of the constituent cells.

Medullated Fibers.—The Weigert-Pal sections show little change in the medullated nerve fibers as compared with the widespread change in their cell bodies. Sections of the cerebral cortex show a slight scarcity of fibers in the tangential layers, but the radial fibers show little if any change. A similar preservation of the medullary fibers is found in the optic nerve, olfactory bulb and in the optic chiasma immediately posterior to the decussation. In the cervical cord a few degenerated fibers are found in the lateral columns in the region of the crossed pyramidal tracts.

Neuroglia.—The neuroglia shows little evidence of proliferation in any of the regions examined. The greatest increase is found in the molecular layer of the cortex, especially in the frontal regions where the atrophy of the convolutions is most marked. Here a dense network of glia fibrils is seen, which is increased in thickness just below the pia.

Lipoids.—The subject of the lipoids of the nervous system and their "Abbon" products is too extensive to be thoroughly considered in this brief report. A brief description of the more important findings will be given.

The more universal stains for lipoids, such as Sudan III or Scharlach R, give the best general picture of the state of these fatty substances in the diseased nervous systems. The "inflated" degenerated areas in the ganglion cells, as described above, are filled with a fine granular fatty substance which stains a light orange yellow.

Scattered among the medullated fibers are other cells which contain rather larger deeper orange staining droplets in varying numbers.

The number of such cells varies widely in different regions, being especially numerous in the cerebellum. They are most likely the glia cells described by many authors (Merzbach, Alzheimer) as *Abraumzellen.*

Still other cells filled even to a greater extent with intensely staining orange red droplets are seen grouped around the perivascular lymph spaces. These cells are crowded with droplets of all sizes, so that their nuclei are obscured. These are the "adventitial cells" of Marchand, or in some part the emigrated glia *Abraumzellen.*

By means of the various differential stains for fat a rough microchemical determination of the nature of the fat can be made. It is found that the lipoidal substance in the degenerated ganglion cells is related to the phosphorus containing phosphatids or lipins (Leathes) of which the so-called "lecithin" is an example. The simpler fats, such as neutral fatty esters and fatty acids, are found only in the adventitial cells surrounding the perivascular lymph spaces. The glia cells show an indefinite intermediate reaction which may be interpreted as a midstage in the breaking down of the more complex lipoids. A large number of these glia cells contain double refractive fats, which give the typical "Maltese cross" with crossed Nicol's prisms. A small amount of such doubly refractive fats is found in the adventitial cells. It would seem most likely that in these anisotropic lipoids we have to do with cholesterin esters or cholesterin mixtures.

The chemistry of the brain lipoids is one of the most complicated fields of the biochemical sciences, and as our knowledge of microchemical reactions is very incomplete, it is difficult to draw any definite conclusions as to the chemical changes which are progressing in these diseased nervous systems. We are, however, warranted in saying that there is a demonstrable breaking down of the complex lipoids (phosphorus and nitrogen-containing lipins) into their simpler components (neutral fats, fatty acids and cholesterin compounds) and that the glia and adventitial cells play an important part in this process. It is interesting to note that Mott and others have described an increase in the cholin content of the blood in cases of amaurotic idiocy, so offering a possible explanation of the removal of the phosphorus and nitrogenous constituents of the lipins (phosphatids).

It is unlikely that the above described changes in the lipoids are in any way characteristic of amaurotic idiocy, for similar processes would be expected in all affections of the nervous system in which degeneration of nervous elements plays an important rôle. A further study of various degenerative conditions is in progress and will be reported in greater detail at a later date.

Pathologically our case agrees in all essential details with the reports found in the literature. We would call especial attention to the fact that there is an equal agreement with the descriptions of the infantile type of the disease. Sachs[24] in speaking of this relation says, "While there is a superficial resemblance between the cell changes in these two varieties of amaurotic idiocy, the differences are still more striking. In the juvenile form the disease is not so universal as in the infantile and we fail to find the typical balloon-like enlargement of the cell bodies and the swelling of the dendrites so characteristic of the cells of the Tay-Sachs type." In the present case of the juvenile type we find all these changes mentioned by Sachs.

It is interesting to note a recent study of an infantile case by Savini-Castano and Savini[25] in which a very extensive discussion of the etiology, pathogenesis and pathologic anatomy is given, with a review of the literature to date. Their findings are in a sense a reversal to the original conception of Sachs, in that they describe a "Bildungshemmung" of the myelinated fibers. They therefore consider the condition a degenerative process which has affected an undeveloped nervous system. This last they assume from the lack of differentiation in the layers of the cerebral cortex, the lack of differentiation of the various regions of the cortex, and the failure of myelinization of the nerve fibers.

The present case, however, furnishes further confirmation to the conception that the disease is a degenerative process affecting a nervous system lowered in resistance or in vitality. As we have no morphologic evidence of congenital abnormality, either gross or microscopic, it would seem that it is the lowered vitality which is transmitted at birth, and these cells of weakened resistance suffer at a later date from the effects of some toxic agent as yet unknown.

2502 Fillmore Street.

Other contributions to the literature on this subject are the following:

Sachs, B.: Jour. Nerv. and Ment. Dis., 1892, xix, 603.
Sachs, B.: Deutsch. Med. Wchnschr., 1898, xxiv, 33.
Jacobi: Arch. Pediat., 1898, xv, 561.
Holden: Jour. Nerv. and Ment. Dis., 1898, xxv, 550.
Clairborne: Arch. Pediat., 1900, x, 3.
Higier: Deutsch. Ztschr. f. Nervenheilk., xxxi, 231.
Higier: Deutsch. Ztschr. f. Nervenheilk, xxxviii, 388.
Holmes, G.: Brain, 1906, xxix, 180.
Gifford: Ophth. Rec., 1912, xxi, 577.
Stewart: Rev. Neurol. and Psychiat., Edinburgh, 1912, x, 351.
Smith, R. M.: Boston Med. and Surg. Jour., 1912, clxvi, 376.
Spiller: Am. Jour. Med. Sc., 1905, cxxix, 40.

---

24. Sachs: Jour. Exper. Med., 1910, xii, 685.
25. Savini-Castano: Ztschr. f. Kinderheilk., Orig., 1913, vii, 321.

STUDIES ON THE CIRCULATION IN MAN

XIII. THE BLOOD FLOW IN THE HANDS AND FEET IN CERTAIN DISEASES OF THE NERVOUS SYSTEM *

G. N. STEWART, M.D.
CLEVELAND

The study of the blood flow in the hands and feet is of special interest in diseases of the nervous system, in which the extremities are so often involved. The skeletal reflexes are so frequently affected that it seemed of some consequence to explore also the vasomotor reflexes by the method described in previous papers.[1] A preliminary account of some of the work was given in a Harvey Lecture.[2] The material available of course allowed a more complete study of some conditions than of others. Also, in a first survey, those conditions were naturally selected in which changes in the blood flow or in the vascular reflexes seemed most likely to be detected, and if detected to be capable of being most clearly related to the symptoms and morbid anatomy of the diseased states. Such conditions as affected only one side (hemiplegia, unilateral peripheral neuritis) were obviously of interest not only in connection with the pathologic physiology of the circulation, but also as affording the opportunity of testing still further the technic of the method, since they permitted the direct comparison of a normal part with the corresponding diseased part.

For one or other of these reasons it happens that most of the material studied in this paper falls under one of three heads: (1) Peripheral neuritis (due to trauma, rheumatism, alcohol, etc.); a case or two in which the condition was probably neuralgia rather than neuritis is included in this group; (2) cerebral hemorrhage (or obstruction of cerebral vessels) with hemiplegia, and (3) tabes. Some other cases are also introduced mainly for the sake of comparison. These comprise cases of motor neuron disease, cerebral tumor, and gunshot wound of the brain. Some observations, chiefly on the vascular reflexes, were made on patients affected by certain poisons which act especially on the nervous system (alcohol, lead), but in whom at the time of observation no symptoms of actual anatomic lesions (peripheral neuritis) were present. A case of excessive tobacco smoking and a

* Submitted for publication March 25, 1915.

* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Paper II of this series, Heart, 1911, iii, 76; Papers IX, X and XI, The Archives Int. Med., 1913, xii, 678; Ibid., 1914, xiii, 1, 177.

2. Nov. 23, 1912.

patient recovering from tetanus under treatment with antitoxin are also included because the vasomotor reflexes seemed to present points of interest. In one or two instances the blood-flow measurements were applied to the detection of malingering with, it is thought, helpful or at least suggestive results.

PERIPHERAL NEURITIS

In three cases of unilateral brachial neuritis, not of long standing, in which no decided atrophy of the hand had as yet occurred, although the strength of the grip was markedly diminished, the blood flow in the affected hand was conspicuously greater than in the contralateral normal hand. In two of these cases the lesion was on the right side and as has been mentioned in previous papers, normal right-handed persons usually show a slight preponderance in blood flow per 100 c.c. of hand volume on the right side. In the cases referred to, however, the difference was much greater, and one of the cases in which the lesion was on the left side presented an equally large excess in the left hand.

Thus in O. A. H., a man with right brachial neuritis probably of traumatic origin, and not at the time of observation associated with any wasting in the right hand, the flow in the right hand was 8.79 grams and in the left hand 6.99 grams per 100 c.c. of hand per minute, with room temperature 24 C. The ratio of the flows in the two hands (1:1.26) shows a very decided preponderance of flow in the affected hand.

O. A. H., a house carpenter aged 60, was admitted to the dispensary January 25, suffering from right brachial neuritis. Seven years ago he fell from a building on his right shoulder and has always had some pain in shoulder since. For three months he had severe pain and weakness in his shoulder. Pain is felt on pressure over the circumflex and over the median nerve above the elbow, and tenderness over the brachial plexus in neck and axilla. The grip of the right hand is much less strong than that of the left. Slight numbness is the only sensory disturbance. All movements of the right arm are weak, but there is no wasting of the hand. February 24: The systolic blood pressure is 130. No impairment of tactile sensation exists and warmth and cold sensibility is good. Pain sensation is diminished below the elbow. On April 26 his arm was better. The blood flow in the hands was examined January 12, before admission. Hands in bath at 3 p. m.; in calorimeters at 3:10 p. m.; removed from calorimeters at 3:26. 3,050 c.c. of water were in each calorimeter. Room temperature 24.1 C.

In Casimir M., a man aged 27, with left brachial neuritis, the blood flow in the right hand was 5.63 grams, and in the left hand 7.40 grams per 100 c.c. per minute, with an average room temperature of 21.9 C. The ratios of the flows in the two hands is 1:1.31, indicating a great excess in favor of the left hand. The case may fairly be considered an "early" one. Although there was some wasting of the muscles of the left upper arm, and some weakening of the grasp of the left hand,

little if any wasting of the hand as revealed by the volume measurement could be detected.

TABLE 1.—Calorimetric Measurements in Case of O. A. H.

Time	Right	Left	Time	Right	Left
3:00	29.98	29.87	3:21	30.43	30.18
3:12	30.00	29.89	3:22	30.50	30.25
3:13	30.03	29.91	3:23	30.57	30.30
3:14	30.09	29.94	3:24	30.63	30.36
3:15	30.13	29.97	3:25	30.71	30.41
3:16	30.20	30.01	3:26	30.78	30.48
3:17	30.23	30.02	3:35	30.68	30.40
3:19	30.32	30.10	3:51	30.52	30.26
3:20	30.38	30.13			

Cooling of calorimeters in twenty-five minutes, R., 0.26 C., L., 0.22 C. Volume of right hand in calorimeter, 445 c.c. of left 425 c.c. Pulse 80.* Mouth temperature 37.1 C. Room temperature 23.9. He is right handed.†

*Except when otherwise mentioned the pulse rate was always taken in a sitting position.

†It is to be assumed that a patient is right handed unless the contrary is stated.

Casimir M. was admitted to the dispensary, January 4, with left brachial neuritis. He had noticed pain in the left elbow for three months, mostly when at work (as a sewing machine operator). He had had no injury. No local signs were seen at elbow. There was no history of venereal infection. Considerable thickening of the radial artery existed. On January 31 the left arm was still weak and he could not use it properly at work, while there was distinct atrophy of some of its muscles. The circumference of the left upper arm was 24.5 cm., that of right upper arm 26.5 cm., of left forearm 25 cm., and of right 26 cm. Pain on pressure was felt over some of the cervical nerves on the left side, but no pain on pressure over the arm. The grasp of the left hand was weaker than that of the right. On February 17 he felt much better. The blood flow in the hands was examined January 31.

The hands were put into the bath at 3:38½ p. m., into the calorimeters at 3:51, taken out of calorimeters at 4:08. 3,050 c.c. of water were in each calorimeter. Pulse 68. Mouth temperature 36.6 C.

TABLE 2.—Calorimetric Measurements in Case of Casimir M.

Time	Right	Left	Room	Time	Right	Left	Room
3:50	29.40	29.36		4:01	29.58	29.58	
3:52	29.39	29.35	21.7	4:02	29.61	29.62	
3:54	29.42	29.41		4:03	29.64	29.65	
3:55	29.44	29.42		4:04	29.68	29.71	
3:56	29.45	29.43		4:05	29.71	29.75	
3:57	29.47	29.43	22.1	4:06	29.76	29.81	
3:58	29.49	29.48		4:07	29.78	29.83	21.9
3:59	29.52	29.51		4:08	29.80	29.86	
4:00	29.55	29.53		4:27	29.56	29.63	

Cooling of calorimeters in nineteen minutes, R., 0.24 C., L., 0.23 C. Volume of right hand 400 c.c., of left hand 370 c.c.

In John S., a man with right brachial neuritis and distinct weakening although no definite wasting of the right hand, the flows were 10.29 grams and 7.66 grams per 100 c.c. per minute in the right and

left hands respectively, with room temperature 22.3 C. The ratio of the flows (1:1.34) denotes a great preponderance of flow in the hand affected by the lesion. On immersion of the left hand in cold water the flow in the right sank to 5.18 grams per 100 c.c. per minute for the first four minutes and then rose to 8.16 grams per 100 c.c. per minute for the remaining five minutes of the period of immersion. On immersing the left hand in warm water the flow in the right hand mounted to 10.16 grams, which was scarcely equal to the initial flow. This indicates that the flow in the right hand at the beginning of the observation was probably already associated with a considerable vasodilatation on which it was easy to impose a decided reflex vasoconstriction but not an additional vasodilatation.

John S., a bricklayer aged 45, was admitted to the dispensary on February 27 with neuritis in the right arm. He had had pain in right elbow for four weeks, unaccompanied by heat or swelling, and the arm had lost strength. The grip of the right hand was much weaker than that of the left. Tenderness was felt over the external condyle, and very slight tenderness over the right brachial plexus. He attributed the condition to cold. March 6, his condition was the same. The blood flow in the hands was examined February 27.

The hands were put into the bath at 2:50 p. m., into the calorimeters* at 3, removed from calorimeters at 3:37. At 3:15 the left hand was immersed in water at 9 C., and at 3:24 in water at 43 C. At 3:31 the left hand was dried and wrapped up. Pulse 74. Mouth temperature 36.74 C.

TABLE 3.—Calorimetric Measurements in Case of John S.

Time	Right	Left	Room	Time	Right	Left	Room
2:59½	29.61	29.50		3:20	30.57		
3:02	29.69	29.55	23.3	3:21	30.61		
3:03	29.72	29.59		3:22	30.66		
3:04	29.78	29.63		3:23	30.69		
3:05	29.84	29.67		3:24	30.73		
3:06	29.90	29.71		3:25	30.77	.....	23.3
3:07	29.96	29.75		3:26	30.81		
3:08	30.02	29.83	23.4	3:27	30.87		
3:09	30.09	29.88		3:28	30.91		
3:10	30.16	29.92		3:29	30.97		
3:11	30.21	29.96		3:30	31.02		
3:12	30.28	30.03		3:31	31.08		
3:13	30.33	30.06		3:32	31.11		
3:14	30.39	30.11	22.8	3:33	31.14		
3:15	30.45	30.15		3:34	31.19	.....	22.9
3:16	30.48			3:35	31.23		
3:17	30.50	.....	23.3	3:36	31.27		
3:18	30.52			3:37	31.30		
3:19	30.53			3:43	31.22	29.91	

Volume of right hand 412 c.c., of left hand 402 c.c. Cooling of calorimeters, R., 0.08 C. in six minutes, L., 0.24 C. in twenty-eight minutes.

The most natural explanation of the preponderance in the flow on the side of the lesion is that the vasoconstrictor fibers are involved in the neuritis, with a resultant diminution of the vasomotor tone of the hand. It is difficult to see how a neuritis due to trauma or to pressure

* As always, unless otherwise stated, the quantity of water in each hand calorimeter was 3,015 c.c.

could fail to affect these fibers. Nor is there any evidence that they escape completely in other forms of peripheral neuritis although, until it is eliminated by proof to the contrary, the possibility must be granted that a particular poison may spare the efferent vasomotor fibers in the peripheral nerves which it attacks. In a peripheral neuritis involving the vasocontrictors these need not of course be totally incapable of conduction any more than the motor fibers of the part. In the case of John S., for example, it is evident they were not completely paralyzed, since a good reflex vasoconstriction was obtained when the contralateral hand was put into cold water. There is some indication, however, that such a reflex, even when of as great an initial intensity as normal, may be more fleeting than under normal conditions, perhaps because the partially degenerated fibers or their endings are sooner fatigued.

In a fourth case, that of Kaspar J., a man suffering from "early" unilateral brachial neuritis apparently of rheumatic origin, a similar disproportion between the flows in the two hands was noticed, the preponderance being, as before, in favor of the affected hand. Later on, however, in this case practical equality in the flows in the two hands was observed, either because the improvement in the condition had progressed so far at the second examination that the vasomotor tone of the affected hand had again become normal, or possibly because of the action of the salicylates with which he was being treated. At the first examination the flow in the hand on the side of the neuritis (the right) was 4.80 grams per 100 c.c. per minute (allowing for the swelling of the hand) and in the left 3.58 grams, the ratio being 1 :1.34, with room temperature 24.2 C. These flows are subnormal, which may of course be due to the man's general condition, recovering as he was from an acute illness (rheumatic fever). The heart was probably to some extent handicapped. Also arteriosclerosis was present, which is always associated with a subnormal hand flow.[3]

At the second examination with a somewhat higher room temperature (25.3 C.) the flow was practically the same in the left hand (3.72 grams) but in the right hand it was reduced almost to equality with that in the left (3.76 grams per 100 c.c. per minute). The fact that the flow in the left hand remained so low in spite of the relatively high room temperature seems to indicate a great tendency to vasoconstriction. If this were the case we should expect that the preponderance of flow previously observed in the right hand, which by hypothesis was due to diminution, though not to paralysis, of vasoconstrictor tone, should tend to disappear. The slight tendency to vasodilatation is indicated clearly by the tests of the vasomotor reflexes. During immer-

3. Paper XI of this series, THE ARCHIVES INT. MED., 1914, xiii, 177.

sion of the left hand in warm water the flow in the right sank to 2.68 grams per 100 c.c. per minute for the first four minutes of immersion and only reached 4.12 grams per 100 c.c. per minute for the remaining seven minutes. For the first three minutes of immersion of the left hand in cold water the flow in the right was 2.74 grams and for the remaining six minutes 3.75 grams per 100 c.c. per minute. The marked slowing of the pulse rate (57 per minute as compared with 92 at the previous examination), in spite of the higher room temperature and the unchanged body temperature, may be associated with the tendency to peripheral vasoconstriction.

Kaspar J., a laborer, aged 50, was admitted to Lakeside Hospital, April 12, with rheumatic fever. Two weeks before, he began to have severe pain in the left ankle and knee, later in the right knee. Five days before admission the right elbow, wrist, and later the shoulder began to trouble him. The heart sounds were clear; the pulse regular in rate, but irregular in amplitude. The vessel wall was palpable. On April 20 the legs were well, but the right upper arm was still sensitive and much atrophied. On April 30 there was very little pain, but movement of the right arm was much impaired; analgesia existed over the entire right arm. The blood flow in the hands was examined May 5 and again May 8. The grip of the right hand was still weak; pain was felt over the right brachial plexus. Convalescence was uninterrupted and he was discharged May 12.

The hands were put into the bath at 2:36½ p. m., into the calorimeters at 2:46½. At 2:56½ the left hand was put into water at 43 C. At 3:04 the left hand was put into water at 9.5 C. He felt the cold water painful. At 3:13 the right hand was removed from the calorimeter. Pulse 92. Mouth temperature 36.7.

TABLE 4.—First Blood Flow Examination of Kasper J.

Time	Right	Left	Room	Time	Right	Left	Room
2:45	29.65	29.56		3:02	30.095	.....	24.25
2:48	29.67	29.57		3:03	30.13		
2:49	29.69	39.60		3:04	30.175		
2:50	29.71	29.62		3:05	30.20	.....	24.4
2:51	29.75	29.63		3:06	30.215		
2:52	29.78	29.64		3:07	30.24		
2:53	29.80	29.67		3:08	30.28		
2:54	29.84	29.70		3:09	30.31		
2:55	29.88	29.72	24.2	3:10	30.34	.....	24.4
2:56	29.90	29.74		3:11	30.37		
2:57	29.93	29.76		3:12	30.40		
2:58	29.965			3:13	30.44		
2:59	29.95	.....	24.2	3:21	.....	29.57	
3:00	30.03			3:22	30.34		
3:01	30.07						

Volume of right hand 511 c.c., of left 457 c.c. The right hand is still somewhat swollen and noticeably larger than the left. Cooling of calorimeters, R., 0.10 C. in nine minutes, L., 0.19 C. in twenty-four minutes.

The particulars of the second examination of Kasper J. are given in the general table.

In a fifth case (John McH.), although symptoms described by the patient suggested a right brachial neuritis, the suspicion of malingering could not be excluded. The flow in the right hand was 4.30 grams

and in the left 3.91 grams per 100 c.c. per minute with room temperature at 23.3 C. The ratio of the flow of the two hands is 1:1.1. On the following day another examination was made and the flows came out 5.46 grams and 4.74 grams for the right and left hands respectively with the same room temperature, a ratio of 1:1.15. Immersion of the left hand in warm water caused a marked vasoconstriction in the right hand for the first six minutes, reducing the flow to 3.23 grams per 100 c.c. per minute. This was succeeded by a moderate vasodilatation (for the remaining seven minutes of the period of immersion of the left hand) the flow in the right hand increasing to 6.11 grams.

John McH., a laborer, aged 58, was admitted to the City Hospital, June 4, apparently suffering from right brachial neuritis. He complained of stinging and numbness of right forearm and hand, especially the middle finger. He had been addicted to alcohol and had several attacks of delirium tremens. There was pain on pressure over the right shoulder, at the inner side and front of the head of the humerus. He could raise his right arm slowly and apparently with some pain to the horizontal position but not higher. His hands felt cold. He said he was cold all over. He stated that he sometimes had sudden swelling of the back of the right hand, which disappeared in a few minutes. He had no trouble in walking but said he was "very irritable and twitched a great deal." There seemed to be a considerable mental factor in the case and a possibility of malingering. The pain and tingling did not inconvenience him, but he feared they might be premonitory of a "stroke." Blood flow in hands was examined on June 5 and again on June 6. Particulars of the first blood-flow examination are given in the general table.

TABLE 5.—Calorimetric Measurements in Second Examination of John McH.

Time	Right	Left	Room	Time	Right	Left	Room
2:40	31.40	31.31		3:00	31.80	31.66	
2:42	31.39	31.31		3:01	31.835	31.695	
2:43	31.40	31.32		3:02	31.85	31.71	23.15
2:44	31.41	31.33	23.1	3:03	31.88	31.72	
2:45	31.425	31.35		3:04	31.88	.....	22.9
2:46	31.46	31.375		3:05	31.89		
2:47	31.49	31.41	23.1	3:06	31.90		
2:48	31.52	31.425		3:07	31.91		
2:49	31.54	31.44	23.2	3:08	31.925	.....	22.9
2:50	31.575	31.46		3:09	31.935		
2:51	31.59	31.48		3:10	31.965		
2:52	31.60	31.49	23.2	3:11	31.99	.....	23.05
2:53	31.625	31.52		3:12	32.02		
2:54	31.66	31.54		3:13	32.045		
2:55	31.68	31.55	23.4	3:14	32.075		
2:56	31.71	31.58		3:15	32.09	.....	23.0
2:57	31.75	31.625		3:16	32.12		
2:58*	31.78	31.635	23.2	3:39	31.82	31.29	
2:59	31.795	31.65					

Cooling of calorimeters, R., 0.30 C. in twenty-three minutes, L., 0.43 C. in thirty-six minutes. Rectal temperature 37.5 C. Volume of right hand 512 c.c., of left 491 c.c. Water equivalent of calorimeters with contents, R., 3,504, L., 3,488. Blood pressure left arm, systolic 116, 93 (sound gone). Right arm, 115, 93.

* Here he heard warm water ordered and became anxious.

At the second examination the patient says the pain in the right shoulder is rather worse than yesterday. The hands were placed in bath at 2:32 p. m., in the calorimeters at 2:41½, taken out of calorimeters at 3:16. Pulse 88. At 3:03 left hand was put into water at 43 C.

While it would of course be absurd to claim that such observations would of themselves be sufficient to justify a diagnosis of malingering in this case the slight difference in the flows in the two hands, scarcely exceeding if at all that often observed in normal persons, suggested that if the symptoms described were genuine they were due rather to a functional than to a structural lesion—to a brachial neuralgia rather than to an "early" brachial neuritis. In the period during which the patient was still under observation the condition did not develop further and he was discharged "improved" a very few days after the last examination. There is little doubt that in cases in which certain neurologic conditions are simulated a measurement of the blood flow might sometimes help to clear up the diagnosis. In long-standing paralyses whether due to a peripheral or to a central lesion there is a decided diminution in the blood flow of the affected hand (or foot) as compared with the normal part.

Thus, in a case of long-standing brachial neuritis of the right side associated with cervical rib (Mrs. M. C.) the flow was much smaller in the affected than in the normal hand (3.98 grams per 100 c.c. per minute in the right, and 5.70 grams in the left hand) the ratio being 1:1.43, with room temperature 23.5 C.). This agreed with the statement of the patient that the right hand was always colder than the left. There was slight wasting of the right hand, only clearly revealed by measurement of the volume, but the hand was little used. The atrophy chiefly affected the proximal segments of the limb. Here it may be supposed that the nerve lesion has led to anatomic changes in the blood vessels causing a narrowing of their lumen.[4]

Mrs. M. C., aged 38, was admitted to the dispensary in April, 1910. She states that in her fourteenth year she worked very hard in a hayfield on a hot day, had sunstroke and fell unconscious. When she recovered consciousness, right arm and shoulder were aching and there was some loss of power there. This has gone on gradually increasing. Continuous pains have been in the right shoulder for the past three weeks. There is exostosis of the scapula (curved scapula) and a marked prominence in right supraclavicular region extending upward and forward for two inches and pressing on the brachial plexus. Cervical ribs were shown by Roentgen ray. Extreme tenderness was felt on pressure in supraclavicular region. Atrophy and weakness were noted of the serratus magnus, infraspinatus, supraspinatus, and latissimus dorsi. The deltoid and other muscles of the arm and forearm show weakness and slight atrophy. There was no apparent wasting of the right forearm or hand, although she does not now use them much. The grip of the right hand was fairly strong, although weaker than the left. She was right handed. There

4. Todd: Jour. Nerv. and Ment. Dis., 1913, xl, 439.

was a marked diminution of sensation to pricking and to contact with camel's hair brush over right shoulder. Over arm and forearm sensation is normal. Blood flow in hands was examined Feb. 14, 1911.

Hands in bath at 2:03 p. m., were placed in calorimeters at 3:14, and taken out of calorimeters at 3:29. Pulse 88. Mouth temperature 37.4 C. Room temperature 23.8 C.

TABLE 6.—Calorimetric Measurements in Case of Mrs. M. C.

Time	Right	Left	Time	Right	Left
3:13	30.29	30.27	3:23	30.38	30.46
3:16	30.27	30.27	3:24	30.39	30.48
3:17	30.29	30.31	3:25	30.40	30.50
3:18	30.30	30.33	3:26	30.41	30.51
3:19	30.31	30.34	3:27	30.42	30.52
3:20	30.33	30.38	3:28	30.43	30.55
3:21	30.35	30.41	3:29	30.44	30.57
3:22	30.36	30.43	3:54	30.21	30.34

Cooling of the calorimeters in twenty-five minutes, 0.23 C. Volume of right hand 295 c.c., of left hand 301 c.c.

The possibility of distinguishing a neuralgia from an "early" neuritis by measurement of the blood flow seems to be indicated by such cases as that of Max B., a carpenter, aged 24, in whom the diagnosis of occupational neuralgia (possibly with slight neuritis) was made.

The blood flow came out 13.89 grams per 100 c.c. per minute for the right (the affected) hand and 13.38 grams for the left, with room temperature 24.5 C. (ratio of flows in the two hands 1:1.04). These flows are of a normal order of magnitude for the age and general condition of the patient and the room temperature. The slight preponderance of flow in the right hand is no more than that usually observed in normal right-handed persons. If the condition were a typical "early" neuritis a much greater excess of flow in the affected hand would be expected, owing to paralysis of vasoconstrictors. The vasoconstrictor reflex in the right hand when the left was immersed in cold water was well marked, the flow falling to 7.25 grams for the first three minutes of immersion, but rising again during the remaining six minutes to 10.83 grams per 100 c.c. per minute. Immersion of the left hand in warm water caused a moderate increase in flow in the right (to 12.53 grams per 100 c.c. per minute for the whole period of immersion of seven minutes). The initial value was not reached. The vasomotor reflex to warmth in this experiment differed from that in normal cases and also from that in the cases of undoubted neuritis in this respect, that there was no distinct initial diminution of flow in the right hand when the left was put into the warm water, or a very slight and transient one. There is not enough material, however, to show whether this has any general significance. The protocol of the case has already been published.[5]

5. Cleveland Med. Jour., 1911, x, 398.

One case diagnosed as sciatica of the left leg was examined.

Frank S., a man aged 64, a laborer in a stable, had to sleep about the stable, often on the wet floor. For six weeks previous to admission the leg had been growing rapidly worse. Now he can hardly bear his weight on it. The trouble is worse at night. Both knee-jerks are exaggerated, especially the left. The Achilles jerk is evident on the left side. Some tenderness is present along the nerve trunks of the left leg, which feels cold at times.

At the first examination of the blood flow—three days after admission when the condition was still acute—the flow in the feet was found exceedingly small both absolutely and in proportion to the hand flow, namely, 0.22 gram per 100 c.c. per minute for the right foot, and 0.47 gram for the left, with room temperature 21 C. Immersion of the right foot in warm water caused no increase in the flow in the left foot, which for ten minutes during immersion of the right foot continued at the rate of 0.43 gram per 100 c.c. per minute. The flow in the right hand was 4.20 grams, in the left 4.39 grams, with room temperature 22.1 C. The ratio of the combined foot flows to the combined hand flows was 1:12.4, indicating a marked tendency to vasoconstriction in the feet, possibly due in part to the pain. The fact that in spite of this tendency to vasoconstriction the flow in the left foot is double that in the right would seem to indicate a condition of the nerves of the left leg constituting a partial block for vasoconstrictor impulses. If a condition of neuritis of the large nerve trunks of the leg is present this would agree with the results on cases of brachial neuritis. Twenty-two days later, when the pain in the thigh had disappeared, the flow in the left foot was found somewhat inferior to that in the right, which agreed with the fact that for three or four days previous to the examination he had felt the left foot cold, although it was covered with sweat.

A number of cases of alcoholic neuritis came under observation. A detailed account of the results in one will suffice. A second case is considered in another connection in Paper XII, published in *Journal of Experimental Medicine,* xxii, 1915, No. 1.

Charles de M., a pianist, aged 29, height 6 feet, 1 inch, weight 170 pounds, was admitted to the City Hospital, July 9, with diagnosis of chronic alcoholism with neuritis. He has been drinking since boyhood and drinks a quart of whisky daily. There is no noticeable anemia. The heart and lungs are normal. The liver is palpable. Knee-jerk and tendo Achillis reflex are markedly exaggerated. A musculo-spiral paralysis of the left forearm and wrist with well-marked wrist drop is present. There is tenderness but no atrophy. The left hand is weaker than right; the left foot is also worse than the right. Two months ago there was marked toe-drop in the left foot. He could stand on the right foot alone but not on the left. The toe-drop is not now so bad. A general tremor exists. The maximum temperature on July 11 was 100.6 F. After this it was never above 99.6 F. with a minimum of 97.8 F. The patient sweats freely. He was discharged improved, July 29. The blood flow in the hands

was examined on July 10 and in the feet and hands on July 16. He was unable to walk into the room.

First examination, July 10: Hands in bath at 1:58½ p. m., in calorimeters at 2:08½. At 2:25 the right hand was put into water at 8.1 C., and at 2:35 into water at 43.1 C. He complained much of the cold water. At 2:44 the right hand was taken from the calorimeter. Pulse 68. The day was very warm.

TABLE 7.—Calorimetric Measurements in Case of Charles de M.

Time	Right	Left	Room	Time	Right	Left	Room
2:07	31.325	31.32	30.1	2:27	.....	32.425	
2:09½	31.37	31.36		2:28	.....	32.45	
2:10	31.39	31.39		2:29	.....	32.49	
2:11	31.46	31.45	30.2	2:30	.....	32.55	29.9
2:12	31.505	31.525		2:31	.....	32.60	
2:13	31.57	31.60		2:32	.....	32.64	
2:14	31.63	31.68		2:33	.....	32.695	
2:15	31.685	31.75		2:34	.....	32.73	29.8
2:16	31.75	31.81	30.1	2:35	.....	32.77	
2:17	31.81	31.86		2:36	.....	32.815	
2:18	31.87	31.93		2:37	.....	32.85	
2:19	31.94	32.01		2:38	.....	32.90	29.8
2:20	32.00	32.05		2:39	.....	32.945	
2:21	32.065	32.125	30.0	2:40	.....	32.995	
2:22	32.125	32.18		2:41	.....	33.04	
2:23	32.19	32.26		2:42	.....	33.10	
2:24	32.26	32.32		2:43	.....	33.14	
2:25	32.31	32.365	30.0	2:44	.....	33.20	29.7
2:26½	.....	32.42		2:50	32.17	33.11	

Cooling of calorimeters, R., 0.14 C. in thirty-four minutes, L., 0.09 C. in fifteen minutes. Volume of right hand 488 c.c., of left hand 479 c.c. Rectal temperature 37.5 C. Water equivalent of calorimeters with contents, R., 3,485, L., 3,478. Blood pressure left arm, systolic 118 (palpation), 121 (stethoscope), 74 (sound gone).

Second examination, July 16: The patient's left hand is to-day in a splint on account of wrist-drop. It feels stiff and swollen, probably from the pressure of the splint. He walked into the room without help and feels much better. Hands in bath at 3:07 p. m., were in calorimeters at 3:17, and out of calorimeters at 3:29. Pulse 84. The weather is much colder than at the last examination.

TABLE 8.—Calorimetric Measurements in Second Examination of Charles de M.

Time	Right	Left	Room	Time	Right	Left	Room
3:15	31.40	31.39	24.9	3:25	31.83	31.77	
3:18	31.425	31.405	25.2	3:26	31.90	31.805	25.1
3:19	31.495	31.465		3:27	31.95	31.855	
3:20	31.56	31.51	25.15	3:28	31.99	31.89	
3:22	31.66	31.60		3:29	31.035	31.935	
3:23	31.72	31.66		3:35	31.96	31.86	
3:24	31.79	31.71					

Cooling of calorimeters in six minutes, R., 0.075 C., L., 0.075 C. Volume of right hand 479 c.c., of left hand 494 c.c. Water equivalent of calorimeters with contents, R., 3,478, L., 3,490. Rectal temperature 37.7 C.

At the first examination in Charles de M. the flow in the right hand was 9.96 grams per 100 c.c. per minute, in the left (the weaker of the two hands) 10.76 grams, with the very high room temperature 30.1 C. The ratio between the flows in the two hands was 1:1.08. These flows

are subnormal for his age at this room temperature. Immersion of the right hand in cold water caused a good reflex vasoconstriction, the flow in the left dropping to 5.84 grams per 100 c.c. per minute for the first three minutes, to rise again to 9.45 grams per 100 c.c. per minute for the next seven minutes of the immersion. Immersion of the right hand in warm water caused only a very moderate increase above the initial flow in the left hand (to 11.27 grams).

At the second examination, six days later, the flow was 9.92 grams for the right hand and 8.95 grams for the left with room temperature 25.1 C. These flows are fairly normal for the room temperature, and the patient's condition was much better than at the previous examination. His pulse rate was 84 instead of 68. The deficiency in the flow in the left hand is probably to be attributed to obstruction caused by a splint. But in no patient with alcoholic neuritis examined has the same marked difference between the two hands (or feet) been observed as in the cases of brachial neuritis already described. Two points have to be considered in this relation—first, in alcoholic neuritis the action of the poison is necessarily bilateral, although the neuritis may at a particular time have progressed farther on the one side than on the other. Secondly, if, as appears often to be the case, it is the small muscular branches which are specially affected in alcoholic neuritis, a very marked increase in the blood flow of the hand most affected by the neuritis could scarcely be expected, since the hand flow is above all a cutaneous blood flow.

The flow in the feet at the second examination of Charles de M. came out 0.90 gram per 100 c.c. per minute for the right foot and 1.20 grams for the left. These flows are not only absolutely small, but small in proportion to the hand flows. The preponderance is on the side (left) on which the foot-drop is worse, but in dealing with such small flows, particularly in the case of the feet in which vasoconstriction caused by the necessary manipulations connected with the measurement is not easily avoided in patients specially susceptible to this condition, too much stress must not be laid on small differences. The next case, although the patient was much addicted to alcohol, probably represents a neuritis due to pressure.

Frank D., aged 39, height 5 feet, 11 inches, a school teacher in Germany, since then a casual laborer, was admitted to the City Hospital, July 22, with wrist-drop of left hand. Pronation and supination are perfect. He can palmarflex left hand to some extent but cannot dorsiflex it. He has long been a heavy drinker and has had delirium tremens. Has been sleeping outside. On the morning of July 21 he first noticed that he could not move his left hand. For all he knows he may have been lying on it. He never had anything of the kind before. Some numbness is present on the dorsum of the left hand, especially on the radial side, although pin pricks and contact of the blunt point are felt everywhere. Wrist-jerk is absent on the left side, but is well marked on the right. Knee-jerk is present on both sides. The heart and lungs are normal.

There is no noticeable anemia. He was discharged improved July 27. The blood flow in the hands was examined July 23.

The hands in bath at 1:54 p. m., were in calorimeters at 2:06. Left hand out of calorimeter at 2:47. The right hand was put into cold water (8 C.) at 2:23 p. m. Pulse 76. At 2:34 right hand was put into water at 43 C.

TABLE 9.—Calorimetric Measurements in Case of Frank D.

Time	Right	Left	Room	Time	Right	Left	Room
2:05	31.01	30.97		2:28	.....	32.075	25.1
2:07	31.025	30.985		2:29	.....	32.13	
2:08	31.06	31.01		2:30	.....	32.17	25.05
2:09	31.095	31.05	25.1	2:31	.. ..	32.24	
2:10	31.14	31.08		2:32	.....	32.28	
2:11	31.19	31.11	25.2	2:33	.....	32.325	
2:12	31.235	31.165		2:34	.....	32.35	25.15
2:13	31.30	31.23		2:35	.....	32.365	
2:14	31.38	31.29		2:36	.....	32.37	
2:15	31.43	31.36	25.2	2:37	.....	32.38	
2:16	31.505	31.43		2:38	.....	32.395	25.25
2:17	31.57	31.49		2:39	.....	32.405	
2:18	31.635	31.565		2:40	.....	32.45	
2:19	31.70	31.635		2:41	.....	32.50	
2:20	31.78	31.72		2:42	.....	32.56	
2:21	31.84	31.79	25.2	2:43	.....	32.61	
2:22	31.91	31.86		2:44	.....	32.665	25.2
2:23	31.95	31.94		2:45	.....	32.72	
2:24	.....	31.97		2:46	.....	32.78	
2:25	.....	31.995		2:47	.....	32.845	
2:26	.....	32.01		3:06	31.53	32.62	
2:27	.....	32.05					

Cooling of calorimeters, R., 0.46 C. in forty-three minutes, L., 0.225 C. in nineteen minutes. Volume of right hand, 572 c.c., of left hand 542 c.c. Water equivalent of calorimeters with contents, R., 3,553, L., 3,529. Rectal temperature 37.6 C. Blood pressure left arm systolic 133 (palpation), 133 (stethoscope), 86 (sound gone). Another observation 133, 87.

In the case of Frank D. a slight preponderance of flow in the left hand was observed, 10.18 grams per 100 c.c. per minute for the right hand and 10.54 grams for the left with room temperature 25.2 C. for the last 11 minutes before testing the vasomotor reaction. The ratio of the flows in the two hands is 1:1.03. Immersion of the hand in cold water caused a good and durable vasoconstriction in the left hand. Immersion of the right hand in warm water occasioned a great initial vasoconstriction in the left, lasting for three minutes, during which the flow was reduced to 3.38 grams per 100 c.c. per minute. This gave way suddenly, as is normally the case, to vasodilatation, the flow in the left hand reaching 10.81 grams per 100 c.c. per minute for the remaining eight minutes of immersion of the right in the warm water. It will be observed that the initial flow was only slightly surpassed.

Since in this case the paralysis is confined to one hand, no other part of the body being at all affected, and since it came on suddenly, the conclusion seems justified that it was a pressure palsy. It is known that the long supinator sometimes escapes in pressure paralysis of the musculo-spiral nerve. Obviously cutaneous nerves are only slightly involved, and vasomotor fibers for the cutaneous vessels would not in

this case be affected to any appreciable extent. Moreover it has been stated that the radial nerve does not carry vasomotor fibers.[6]

Although this statement is probably based on too slight an experimental foundation and need not be taken literally, it is clear enough that in the case under consideration a difference in the flow in the two hands comparable to that observed in lesions affecting the brachial plexus could not be expected.

In a case of motor neuron disease without sensory deficiency (Mrs. Mary N.) the vasoconstrictor reflexes were found to be of quite normal intensity and of more than normal duration.

Mrs. Mary N., a tailoress, height 5 feet, 6 inches, aged 46, was admitted to the dispensary, Nov. 10, 1910, suffering from progressive muscular atrophy. Her left hand became very painful about September, 1909. About a month thereafter she noticed some atrophy of the thenar eminence and weakness of the hand. About Christmas, 1909, the right hand became similarly affected. The condition gradually progressed and now the right arm shows some atrophy of the deltoid and musculo-spiral paralysis in the forearm, and wrist-drop with some median paralysis as well. Some atrophy of the thenar eminence exists. On the left side there is atrophy of the thenar eminence and some weakness of flexors and extensors but no wrist-drop. No loss of reflexes is shown in either arm. Both wrists and hands are wasted. The grip of both hands is very weak. The left leg is smaller than right, and has been so, at any rate, from the age of 3. It shows peroneal palsy with foot-drop and shortened Achilles tendon, yet she can walk well. Some pain is present along the spine at the base of the neck. Knee-jerk and Achilles reflex are exaggerated on the right side, absent on the left. Babinski's sign is noted in the left foot. There is no sensory disturbance, clonus, or Romberg's sign. The pupils react to light and accommodation. The blood gives a strongly positive Wassermann reaction. The spinal fluid shows 150 cells per c.c., practically all mononuclear. The Noguchi reaction is positive. Physical examination of thorax is negative. Treatment with mercurials and potassium iodid, also with salvarsan, was without result. The patient continued to come to the dispensary till January, 1913, her condition gradually growing worse.

On March 7, 1912, the blood flow in the hands was examined. Hands in bath at 2:27½ p. m., in calorimeters at 2:38. At 2:52 the right hand was put into water at 8 C. At 3 p. m. right hand was put into water at 43 C., which caused the hand to tingle. At 3:07 right hand was dried and wrapped in warm cloth. At 3:14 right hand was removed from calorimeter. Pulse 116. Mouth temperature 37.6 C.

The blood flow in the right hand was 6.99 grams, and in the left 7.13 grams per 100 c.c. per minute with room temperature 23.6 C. Immersion of the right hand in cold water caused the flow in the left to fall to 3.70 grams. There was no increase during the whole time for which the right hand continued in the cold water (seven minutes). The vasoconstriction was therefore intense and durable. When the right hand was immersed in warm water the flow in the left was further diminished to 3.37 grams. The intensity and persistence of the reflex vasoconstriction in this case may pretty safely be taken to indi-

6. Simons, A.: Arch. f. Anat. u. Physiol., 1910, 559.

cate that the lesion in the motor neurons has not extended to the vasomotor cells in the cord or to the efferent paths from them. Since the pathologic change appears to be a system disease affecting the motor neurons but sparing the sensory neurons, there is nothing strange in its avoiding the vasomotor neurons also.

TABLE 10.—Calorimetric Measurements in Case of Mrs. Mary N.

Time	Right	Left	Room	Time	Right	Left	Room
2:37½	29.62	29.61		2:57	.....	30.13	
2:39	29.60	29.58	23.6	2:58	.....	30.14	
2:40	29.64	29.61		2:59	.....	30.16	
2:41	29.69	29.64		3:00	.....	30.17	
2:42	29.72	29.69		3:01	.....	30.18	
2:43	29.78	29.73		3:02	.....	30.20	
2:44	29.82	29.78	24.0	3:03	.....	30.22	
2:45	29.86	29.82		3:04	.....	30.22	
2:46	29.89	29.86		3:05	.....	30.24	
2:47	29.92	29.90		3:06	.....	30.24	23.9
2:48	29.97	29.93		3:07	.....	30.25	
2:49	30.00	29.96		3:08	.....	30.28	
2:50	30.04	30.00	23.3	3:09	.....	30.30	
2:51	30.07	30.03		3:10	.....	30.33	
2:52	30.10	30.06		3:11	.....	30.36	
2:53	.....	30.07	23.3	3:12	.....	30.37	
2:54	.....	30.09		3:14	.....	30.39	
2:55	.....	30.11		3:15	29.85		
2:56	.....	30.12		3:36	29.64	30.16	

Cooling of calorimeters, R., 0.25 C. in twenty-tree minutes, L., 0.23 C. in twenty-two minutes. Volume of right hand 340 c.c., of left hand 320 c.c.

Another case (Stanislas C.) in which a more or less general atrophy of the extremities, especially the anterior, existed presents certain interesting features. On account of the low degree of intelligence of the patient and his defect of speech the history of the case could not be clearly ascertained. Nor could the defects of sensation which seemed to exist be properly studied. Although this increased the difficulty of making a diagnosis and the true nature of the case was not cleared up, it will not be unprofitable, it is hoped, to quote the blood-flow findings, since they seemed capable of suggesting something toward the diagnosis and of supplementing precisely in such circumstances the examination of the sensory condition.

Stanislas C., a Polish laborer, aged 32, height 5 feet, 6 inches, was admitted to Lakeside Hospital, April 5. The patient complains that he cannot talk properly. Seven months before he was hit by a brick and has since been unable to swallow or talk. He did not lose consciousness. The right supraclavicular region shows a scar from the middle of the clavicle to the top of the scapula. The pupils react promptly to light and accommodation. The mouth tends to be drawn to the right. The tongue protrudes to the right and shows a fine tremor. The soft palate hangs to the right, and the left arch is higher than the right. Blood pressure, 124 systolic, 76 diastolic. General atrophy of muscles of extremities is shown. There is some contracture of the fingers of the right hand. No edema exists. Atrophy is noted of the muscles of the neck; the trapezius, splenii, levator scapulae and serrati. His gait is shuffling but not ataxic. There is no hypotonus of the thigh. All the deep reflexes are exaggerated, except those of the right arm, in which the biceps, triceps and supinator reflexes are gone. There is ankle clonus, but no Babinski or Kernig's sign. Romberg's sign is

very slight. The abdominal and cremasteric reflexes are increased. The right arm is smaller than the left, but the volume measurement showed the left *hand* somewhat atrophied in comparison with the right. Paresis is apparent of the left facial muscles. When asked to smile, the mouth is drawn to the right, but when made to laugh spontaneously both sides are equally used. The right side of the forehead wrinkles more than the left. The vocal cords move very poorly. Then sense of taste is disturbed. His intelligence is very low and does not permit satisfactory examination of sensation. He says that all sensations (temperature, pain, touch, vibration) are better felt over the right side (arm, leg and trunk) than over the left. It is doubtful whether this is true.

The blood flow in the hands was examined April 19. Hands were in bath at 2:25 p. m., in calorimeters at 2:39. Mouth temperature 36.8 C. Pulse 72. At 2:50½ p. m. the left hand was immersed in water at 12 C. At 2:55½ p. m. the left hand was dried and wrapped up. At 2.59⅙ p. m. the left hand was put into water at 43.5 C. At 3:06 the left hand was put into water at 9 C. At 3:13 left hand was dried and wrapped up. At 3:17 right hand was removed from calorimeter.

TABLE 11.—Calorimetric Measurements in Case of Stanislas C.

Time	Right	Left	Room	Time	Right	Left	Room
2:38	29.90	29.93		3:00	30.80	.....	23.5
2:40	29.91	29.89	23.7	3:01	30.87		
2:41	29.94	29.90		3:02	30.94		
2:42	29.97	29.89		3:03	30.99	.....	23.6
2:43	29.99	29.90		3:04	31.07		
2:44	30.02	29.90		3:05	31.12		
2:45	30.07	29.90	23.8	3:06	31.18		
2:46	30.10	29.91		3:07	31.22	.....	23.7
2:47	30.17	29.91	23.6	3:08	31.27		
2:48	30.21	29.91		3:09	31.32		
2:49	30.25	29.92	23.6	3:10	31.39		
2:50	30.30	29.92		3:11	31.45		
2:51	30.35	.....	23.8	3:12	31.49		
2:52	30.39			3:13	31.56	.....	23.6
2:53	30.43			3:14	31.60		
2:54	30.49	.....	23.7	3:15	31.65	.....	23.5
2:55	30.57			3:16	31.70		
2:56	30.60			3:17	31.77	.....	23.5
2:57	30.65			3:17½	.....	29.68	
2:58	30.71	.....	23.6	3:28	31.63	29.60	
2:59	30.78						

Cooling of calorimeters, R., 0.14 C. in eleven minutes, L., 0.32 C. in thirty-eight minutes. Volume of right hand in calorimeter 486 c.c., of left hand 422 c.c.

The flow in the right hand came out 7.0 grams and in the left only 1.47 grams per 100 c.c. per minute (for six minutes before the vasomotor test) the greatest difference between the two hands which has been observed in the whole series of observations. Measurement showed that the left hand was atrophied in comparison with the right. On immersing the left hand in cold water (for four minutes) the flow in the right increased to 7.85 grams per 100 c.c. per minute. When the left hand was dried and wrapped up, the flow in the right hand rose to 9.55 grams, to increase further to 10.28 grams on immersion of the left hand in warm water. A subsequent immersion of the left hand in cold water produced no effect on the flow unless to keep it stationary, and when the left hand was again wrapped up the flow in the right increased to 10.88 grams. These anomalous results in the reflex vaso-

motor tests have scarcely any parallel in our series of observations. The most obvious explanation would be that the left hand was insensitive to cold, and the entire passivity of the patient when the hand was immersed in water at 9 C., which usually produces some discomfort, lends support to the suggestion. The initial vasoconstriction produced by immersion of the contralateral hand in warm water was also absent in this case, and again the suggestion is plausible that the left hand was insensible to warmth. The steady increase in the flow of the right hand during the whole course of the vasomotor tests would then be due simply to a spontaneously increasing vasodilatation unaffected by impulses from the left hand. While it would be rash to lay stress on isolated observations of this kind, it may be further pointed out that the marked deficiency of the blood flow in the left hand as compared with the right would agree well with a suggestion made when the diagnosis was being considered, that the general condition was superposed on an old left-side hemiplegia. For as we shall see directly, in the hemiplegias examined there was always a deficiency in blood flow in the paralyzed hand. The paresis of the left side of the face would also fit in with this. On the other hand the apparent absence of reflex vasomotor response in the right hand when the left was immersed in warm or cold water would agree with another suggestion made, that a syringomyelia (of the bulb) existed. In any case it seems reasonably clear that in circumstances in which the subjective response of the patient to warmth and cold cannot be studied information might be obtained by an objective method, namely, the study of the vasomotor reflex response.

HEMIPLEGIA

In the four cases of hemiplegia examined the flow in the paralyzed hand was always inferior to that in the normal hand. In C., a man aged 57, with hemiplegia of nine years' standing (paralysis of the left side of the face, left arm and leg) from which there had been very little recovery, the flow in the right hand was 9.15 grams and in the left only 4.67 grams per 100 c.c. per minute, with room temperature 22.2 C. During immersion of the right hand in warm water the flow in the left was 4.31 grams per 100 c.c. per minute for a period of nine minutes, and exactly the same during immersion of the right hand in cold water for a period of seven minutes. In this case there was no question of any defect of conduction in the afferent segment of the reflex vasomotor arc, since it was the normal hand which was subjected to the warmth and cold stimulation, and these sensations were perfectly perceived. The absence of the vasomotor reflex in this old-standing paralysis was interpreted as probably due to anatomic changes in the vessels of the atrophied left hand, including changes in the efferent

vasomotor nerves of the hand and their terminations. The protocol of the case has already been published.[7] In the other cases of hemiplegia in which the vasomotor reflexes were examined, evidence was obtained of the activity of the vasomotors of the paralyzed hand, reflex vasoconstriction, however, predominating over reflex vasodilatation.

Mrs. Eva M., aged 56, was admitted to the City Hospital, Sept. 11, 1911, with hemiplegia (left side). On September 5 she lost control of left hand, arm, and leg; fell to the floor but was at no time unconscious and retained the power of speech. When admitted the patient's face seemed unaffected; the tongue protruded in the median line. There was no paralysis of the palate. Complete loss of power and marked loss of tone in arm and leg were noted. The biceps and triceps reflexes of the left arm were absent. The knee-jerk was absent. Babinski's sign was present on the left side. Sense of position was lost in the left arm and leg. The sense of heat and cold was intact in the left arm and left leg above a level 4 cm. below the knee. Pain sense was lost in the left arm below the shoulder and in the left leg below the knee. Some loss of pain sensibility was found between the left knee and the hip.

The blood flow in the hands was examined April 16, 1912. At this time there had been noticeable improvement in the left leg, but not in the arm or hand. The hands were in bath at 3:21 p. m., in calorimeters at 3:32, out of calorimeters at 3:52. Mouth temperature 37.45 C. Pulse 104. The left hand as it hung down in the water pained her somewhat and therefore the vasomotor reaction was not tested.

TABLE 12.—Calorimetric Measurements in Case of Mrs. Eva M.

Time	Right	Left	Room	Time	Right	Left	Room
3:33	30.53	30.41	23.7	3:44	30.76	30.58	
3:34	30.50	30.43		3:45	30.79	30.60	23.3
3:35	30.55	30.46		3:46	30.81	30.61	
3:36	30.59	30.48		3:47	30.845	30.63	
3:37	30.62	30.50		3:48	30.88	30.645	
3:38	30.635	30.52	22.7	3:49	30.90	30.66	
3:39	30.65	30.525		3:50	30.93	30.68	
3:40	30.67	30.53		3:51	30.95	30.70	
3:41	30.69	30.535		3:52	30.99	30.73	
3:42	30.70	30.54		4:02	30.88	30.63	
3:43	30.72	30.555					

Cooling of calorimeters in ten minutes, R., 0.11 C., L., 0.10 C. Volume of right hand 334 c.c., of left hand 328 c.c. Water equivalent of calorimeters with contents, R., 3,362, L., 3,357.

The flow in the right hand in Mrs. Eva M. was 6.30 grams and in the paralyzed left hand 4.38 grams per 100 c.c. per minute with average room temperature 23 C.

George H., a man aged about 40 years, with typical motor aphasia and paralysis of the right arm and leg of 4 years' standing, had a blood flow of 7.26 grams per 100 c.c. per minute in the right hand and 9.82 grams in the left hand with room temperature 26.5 C. The ratio between the flows in the two hands was 1:1.35. During immersion of the left hand in cold water the flow in the right hand sank to 5.04 grams for the first three minutes and then increased to 7.93 grams per

7. Heart, 1911, iii, 81.

100 c.c. per minute for the next seven minutes. Immersion of the left hand in warm water coincided with a further and persistent diminution of the flow in the right to 5.74 grams. It is possible that the vasoconstriction was merely that not infrequently seen at the close of an experiment and does not represent an abnormally great prolongation of the initial vasoconstriction produced by the application of warmth to the contralateral hand. But the duration of the experiment was by no means great and it is at the end of long experiments that spontaneous and long-lasting diminution in the flow is apt to be witnessed. It seems more probable that there is an abnormal tendency to vasoconstriction in the paralyzed hand.

A week later, the flow was again measured in George H. and came out 9.38 grams for the right hand, and 13.21 grams for the left with room temperature 25.5 C. The ratio between the flows was 1:1.40, practically the same as at the previous examination. This indicates that the increase in the flow was due mainly at least to increased action of the heart and it is rather curious that the ratio of the pulse frequencies (1:1.26) agrees almost exactly with the ratio of the blood flows in the paralyzed hand at the two examinations (1:1.29). If the hand flows in this patient can be taken as an index of the heart output, which is justifiable at any rate so far as the absence of anemia is concerned,[8] this result would support the conclusion of Yandell Henderson[9] that with slow heart rates the minute output is proportional to the pulse frequency. There is no reason for thinking that the increased hand flows are due to a vasodilatation affecting the two hands in exactly the same proportion. In any case the external temperature could not be responsible for such an increase as it was about a degree lower at the second examination.

The flow in the feet of George H. was also examined on July 25, and came out 1.63 grams per 100 c.c. per minute for the right foot and 1.77 grams for the left. These flows in proportion to the hand flows are considerably below the normal.

George H. was admitted to the City Hospital, Oct. 5, 1909, with motor aphasia and paralysis of right arm and leg. He became paralyzed in 1908. When admitted he was unable to protrude the tongue. The right side of chest was markedly smaller than the left. There was a slight increase in the deep reflexes in the right arm and leg. The spinal fluid, 40 drops to minute, was clear, with 2 to 4 white cells to the c.c. and no Noguchi reaction. The blood flow in the hands was examined on July 18, and in the hands and feet on July 25, 1912. At this time aphasia is still complete. He seems to understand everything, but can only express assent or dissent by gestures. He can lift his arm to some extent but cannot move his left hand. He walks with a crutch and can stand by holding the back of a chair slightly. He can protrude the tongue easily in the median line and he can write. The knee-jerk is stronger on the

8. Jour. Exper. Med., 1913, xviii, 113.
9. Am. Jour. Physiol., 1913, xxxi, 288.

right side than on the left. Ankle clonus is present on the right but not on the left side. There is no defect of sensation. Some external squint of right eye and diplopia is present. No ptosis exists.

Blood flow examination of George H., July 18, 1912: Hands were in bath at 2:04 p. m., in calorimeters at 2:15. Some minutes elapsed before the right hand was got properly into the calorimeter. At 2:31 p. m. left hand was put into water at 8 C. Pulse 68. At 2:41 left hand was put into water at 43 C. At 2:51 right hand was removed from calorimeter.

TABLE 13.—Calorimetric Measurements in Case of George H.

Time	Right	Left	Room	Time	Right	Left	Room
2:14	31.52	31.45	26.5	2:36	32.135		
2:19	31.54	31.64		2:37	32.18		
2:20	31.58	31.68	26.6	2:38	32.22	.....	26.4
2:21	31.61	31.75		2:39	32.25		
2:22	31.64	31.79		2:40	32.28		
2:23	31.69	31.87	26.8	2:41	32.295		
2:24	31.72	31.93		2:42	32.31		
2:25	31.76	31.98		2:43	32.33	.....	26.4
2:26	31.79	32.045		2:44	32.365		
2:27	31.825	32.08	26.7	2:45	32.38		
2:28	31.87	32.14		2:46	32.395	.....	26.4
2:29	31.90	32.175		2:47	32.42		
2:30	31.935	32.24		2:48	32.45		
2:31	31.98	32.28		2:49	32.475		
2:32	32.005			2:50	32.50		
2:33	32.025	.....	26.7	2:51	32.52		
2:34	32.04			3:18	32.25	31.87	
2:35	32.10						

Cooling of calorimeters, R., 0.27 C. in twenty-seven minutes, L., 0.41 C. in forty-seven minutes. Volume of right hand 464 c.c., of left hand 500 c.c. Mouth temperature 36.95 C. Blood pressure left arm, systolic 90, 82 (sound gone). Another observation 92, 85.

Blood flow examination of George H., July 25, 1912: Results on the flow in the feet are given in the general table.

The hands were in bath at 2:46½ p. m., in calorimeters at 2:56, out of calorimeters at 3:09.

TABLE 14.—Calorimetric Measurements in Case of George H.

Time	Right	Left	Room	Time	Right	Left	Room
2:54	31.38	31.36	25.2	3:04	31.75	31.945	25.55
2:57	31.38	31.39		3:05	31.80	32.00	
2:58	31.43	31.47	25.4	3:06	31.85	32.075	25.7
2:59	31.49	31.58		3:07	31.89	32.165	
3:00	31.53	31.65	25.7	3:08	31.91	32.23	25.7
3:01	31.59	31.73		3:09	31.92	32.27	
3:02	31.66	31.795	25.5	3:17	31.82	32.17	
3:03	31.72	31.865					

Cooling of calorimeters in eight minutes, 0.10 C. for R. and L. Volume of right hand 455 c.c., of left 497 c.c. Water equivalent of hand calorimeters and contents, R., 3,459, L., 3,492. Rectal temperature 37.4 C.

Dennis H., a structural iron worker, aged 41, was admitted to the City Hospital, June 19, 1911, with hemiplegia of the left side. Walking along the street on July 15, he fell unconscious and remained so about fifteen minutes. He had been a hard drinker; had gonorrhea and probably lues. No anemia was present (hemoglobin 100 per cent.). The tongue protruded in the median line. The head was held toward the right rather than the left. He was unable to move the left arm and leg. The patellar, Achilles, biceps and triceps reflexes on the left side were exaggerated. No Babinski sign or ankle clonus was

present. Epicritic and protopathic sensations over left leg were gone. Deep sensibility was present. Epicritic, protopathic, and deep sensibility was present in the arm but was greatly diminished. The same was true over the left side of the neck and face. No loss of power was seen in the face. Systolic blood pressure varied from 140 to 118 during the period of observation. On April 11, 1912, the blood flow in the hands was measured. At this time the left leg had recovered considerably, although he still used it very little. The left hand and arm were still quite powerless.

For the first six minutes in the calorimeters the flow in the right hand was 2.84 grams and in the left 1.80 grams per 100 c.c. per minute. During the immersion of the hands in the calorimeters the flow continued to increase gradually in both hands but particularly in the left so that for the whole period of immersion in the calorimeters (seventeen minutes) the flows came out 4.19 grams and 3.75 grams per 100 c.c. per minute for the right and left hands respectively. For the last six minutes of this period the flows were 4.92 grams for the right and 4.80 grams for the left hand. This gradual increase of the flow is observed under two conditions, first, when the flow is permanently small, and secondly, when an initial vasoconstriction is present, due either to nervousness on the part of the patient or to an abnormal sensitiveness of the vasomotor mechanism to the procedures necessarily involved in the measurement. In the case of Dennis H. both of these circumstances probably conspired. That a considerable tendency to vasoconstriction exists in the paralyzed hand was shown in the tests of the vasomotor reflexes. When the right hand was immersed in cold water the flow in the left was reduced from 4.80 grams to 3.49 grams per 100 c.c. per minute for the first seven minutes, to rise to 5.90 grams per 100 c.c. per minute for the remaining seven minutes of immersion of the right hand in the cold water. This constitutes a fair reflex vasoconstriction, particularly considering the small initial flow, and it endures, if anything, longer than normal. The moderate vasodilatation which succeeded was rather diminished than increased by subsequent immersion of the right hand in warm water.

TABES DORSALIS

In the five cases of tabes examined, the flow in both hands and feet was found subnormal, the deficiency being greater in the feet than in the hands. The vasomotor reflexes were quite feeble. The poor reflex response is especially striking when coupled with distinct or even acute perception of the sensations of cold and warmth, as in the case of Joseph S.

Joseph S., a laborer, aged 54, was admitted to the City Hospital, August 5, with tabes dorsalis. He had had pain and "funny feelings" for five years in both legs. Says he cannot feel over the hands or feet, but feels pin pricks somewhat. He also complains of sphincter trouble, and has a history of gonorrhea and lues. The spinal fluid, 120 drops per minute, 200 cells per c.c., shows

a strongly positive Noguchi reaction. The pupils, pin point, react to accommodation. There is little if any reaction to light. The nasal septum is perforated. Heart examination is negative. There is marked arteriosclerosis. Knee-jerk, Achilles and cremasteric reflexes are absent. Romberg sign is marked. Muscular incoordination is shown.

The blood flow in the hands and feet was measured August 7. Pulse 124. Hands in bath at 1:46½ p. m., in calorimeters at 1:57¾ p. m. At 2:12 left hand immersed in water at 8.4 C. He feels that the water is cold and soon begins to complain of it, withdrawing the hand momentarily. At 2:24 left hand put into water at 42.8 C. At 2:35 right hand removed from calorimeter.

TABLE 15.—Calorimetric Measurements in Case of Joseph S.

Time	Right	Left	Room	Time	Right	Left	Room
1:57	31.20	31.13		2:18	31.785	.....	25.0
1:59	31.22	31.15	24.9	2:19	31.81		
2:00	31.26	31.18		2:20	31.83		
2:01	31.295	31.20	25.1	2:21	31.865		
2:02	31.325	31.22		2:22	31.895		
2:03	31.365	31.255		2:23	31.91		
2:04	31.40	31.27	25.0	2:24	31.935		
2:05	31.43	31.295		2:25	31.96	.....	25.0
2:06	31.46	31.315		2:26	31.985		
2:07	31.495	31.35	25.1	2:27	32.00		
2:08	31.52	31.365		2:28	32.025	.....	25.15
2:09	31.56	31.38		2:29	32.05		
2:10	31.58	31.405	25.1	2:30	32.08		
2:11	31.605	31.43		2:31	32.09		
2:12	31.63	31.45		2:32	32.11		
2:13	31.67	.....	25.0	2:33	32.13	.....	25.4
2:14	31.695			2:34	32.16		
2:15	31.705			2:35	32.19		
2:16	31.73			2:45	32.075	31.13	
2:17	31.76						

Cooling of calorimeters, R., 0.115 C. in ten minutes, L., 0.32 C. in thirty-three minutes. Volume of right hand in calorimeter 425 c.c., of left hand 441 c.c. He is right handed, but from the way in which he held his hand, a somewhat smaller proportion of the right hand was in the calorimeter than of the left. This is taken account of in the volume measurement.

The flow in the right foot in this patient was 0.76 gram and in the left foot 0.88 gram per 100 c.c. per minute with the relatively high room temperature 25 C. The flow in the right hand was 5.86 grams and in the left 4.33 grams with the same room temperature. Probably the inequality in the flows in the two hands is not so great as it appears to be. For, as has been mentioned in the protocol, the right hand was not inserted so deeply into the calorimeter as the left, and it has been shown that the flow per unit of volume is greater in the distal than in the proximal portions of the hand, corresponding with the relatively greater surface. However, in our study of diseases of the nervous system there have been numerous instances of the existence of inequalities of flow in the two hands or feet which could not be connected with any known cause. It may indeed be said that such inequalities are common features of those diseases. It has been suggested that vasomotor conditions, probably essentially connected with the pathology

or pathologic physiology of the morbid state, are responsible for these inequalities.[10]

On immersion of the left hand (of Joseph S.) in cold water, which apparently caused him considerable discomfort, the flow in the right was but slightly changed, falling to 5.21 grams per 100 c.c. per minute for the first four minutes and then rising slightly again to 5.43 grams per 100 c.c. per minute for the remaining eight minutes of the immersion. This is truly an insignificant vasoconstrictor reaction. Immersion of the left hand in warm water caused a slight diminution of the flow in the right, to 5.22 grams per 100 c.c. per minute for the first five minutes, which then gave place to a correspondingly slight increase (to 5.48 grams for the next six minutes). Such slight reflex vasomotor effects have certainly rarely been observed in other conditions. It must be noted, however, that decided arteriosclerosis was present in this man and this condition is itself associated with relatively small vasomotor reflexes.[11]

In a case of tabes examined at the dispensary (Abe K.) the hand flows were only 1.27 grams for the right and 1.22 grams for the left, with room temperature 23 C. Probably the circulatory condition noted in the protocol was a factor in the small flow, as there was evidence of some loss of cardiac compensation (cyanosis, edema of legs and feet).

Abe K., a waiter, aged 59, was admitted to the dispensary January 30. Six weeks ago he began to lose his sight and is now almost blind. For two months he has been unsteady on his feet, especially in walking at night. Some exophthalmos is noted. Slight ptosis of both eyes exists. The face and lips are cyanotic. The pupils are irregular, fixed, unequal, with no reaction to light or accommodation. His gait is uncertain, with left foot flapped. The knee-jerk is much diminished. The Achilles reflex is absent. There is no Babinski sign. Edema of feet and legs is present, with hypotonus of muscles. Sensibility to touch, pain, heat and cold is diminished below the knees. The muscle sense is not good. There is incoordination of the hands. There is a slight Romberg sign. Examination of lungs is negative. The heart dulness extends 2 cm. to the left of the nipple line. There is also increase of dulness to the right of the sternum. The aortic second sound is much accentuated. The edge of the liver is palpable 3 finger breadths below the costal margin on deep inspiration. The blood flow in the hands was measured on February 1.

W. B. C., a cigarmaker, aged 57, was admitted to Lakeside Hospital, November 8, with tabes dorsalis. He complains of difficulty in walking and ataxia, most marked in left leg. There are no sensory disturbances, except that he does not feel hot water on his feet unless it is pretty hot. Up to the present illness his eyesight has been good. There is external strabismus of the right eye. The pupils are unequal and irregular and do not react to light, but react to accommodation. Knee-jerk is absent. The hands are ataxic; he has difficulty in buttoning his clothes. Examination of heart and lungs is negative. The blood flow was examined November 11.

10. Paper XII of this series.

11. Stewart, G. N.: The Blood Flow in the Hands and Feet in Certain Diseased Conditions of the Vessels or of Their Nervous Mechanism, THE ARCHIVES INT. MED., 1914, xiii, 177.

The feet were in bath at 2:23 p. m., in calorimeters at 2:36. At 3:07 the left foot was put into water at 44.3 C. He feels it comfortably warm. At 3:19 right foot was taken out of calorimeter. Pulse 84.

TABLE 16.—Calorimetric Measurements in Case of W. B. C.

Time	Right	Left	Room	Time	Right	Left	Room
2:34	31.33	31.26	20.9	3:01	30.97	31.03	22.0
2:37	31.23	31.18	20.9	3:03	30.95	31.01	22.0
2:39	31.22	31.17	20.9	3:05	30.925	30.99	21.9
2:41	31.19	31.155		3:07	30.90	30.98	
2:43	31.17	31.135	20.9	3:09	30.89	.....	21.9
2:45	31.14	31.13	21.2	3:11	30.88	.....	21.8
2:47	31.11	31.10	21.3	3:13	30.865	.....	21.7
2:49	31.09	31.085	21.3	3:15	30.84	.....	21.7
2:51	31.065	31.07	21.35	3:17	30.825		
2:53	31.04	31.06	21.4	3:19	30.81	.....	21.9
2:55	31.03	31.055	21.7	3:21	30.74	30.68	
2:57	31.01	31.05	21.8	3:34	30.52	30.47	
2:59	30.99	31.04	21.8				

Cooling of foot calorimeters in thrirteen minutes, R., 0.22 C., L., 0.21 C. Volume of right foot 925 c.c., of left foot 943 c.c. Water equivalent of feet calorimeters with contents, R., 3,660, L., 3,673.

The hands were in bath at 3:40 p. m., in calorimeters at 3:48¾. At 4:06 the left hand was put into water at 44.7 C. He feels it warm. At 4:20 left hand was put into water at 13 C. He feels it rather cold. Right hand taken out of calorimeter at 4:29 p. m.

TABLE 17.—Calorimetric Measurements in Case of W. B. C.

Time	Right	Left	Room	Time	Right	Left	Room
3:48	31.75	31.76		4:10	31.89	.....	22.9
3:50	31.74	31.75	23.3	4:11	31.89		
3:51	31.73	31.74	23.2	4:12	31.90	.....	22.7
3:52	31.73	31.74		4:13	31.90		
3:53	31.74	31.75	23.2	4:14	31.91	.....	22.8
3:54	31.74	31.75	23.2	4:15	31.93		
3:55	31.75	31.75		4:16	31.95	.....	22.9
3:56	31.76	31.755	23.1	4:17	31.97		
3:57	31.77	31.765		4:18	31.99	.....	22.9
3:58	31.78	31.775		4:19	31.99		
3:59	31.79	31.785	23.0	4:20	32.01		
4:00	31.80	31.80		4:21	32.01	.....	22.8
4:01	31.81	31.82	22.9	4:22	32.02		
4:02	31.82	31.83		4:23	32.03	.....	22.5
4:03	31.835	31.84	22.9	4:24	32.04		
4:04	31.85	31.85		4:25	32.05	.....	22.7
4:05	31.86	31.86	23.0	4:26	32.06		
4:06	31.87	31.86		4:27	32.065	.....	22.5
4:07	31.88			4:28	32.07		
4:08	31.89	.....	23.0	4:29	32.08	.....	22.7
4:09	31.89			4:38	31.95	31.44	

Cooling of hand calorimeters, R., 0.13 C. in nine minutes, L., 0.42 C. in thirty-two minutes. Volume of right hand 380 c.c., of left 388 c.c. Water equivalent of hand calorimeters with contents, R., 3,399, L., 3,405. Rectal temperature 36.90 C.

In W. B. C. the blood flow in the right foot was 0.54 gram and in the left foot 0.87 gram per 100 c.c. per minute with room temperature 21.5 C. During immersion of the left foot (for a period of twelve minutes) in warm water, the flow in the right was 0.75 gram per 100 c.c. per minute. The hand flows before testing the vasomotor reaction

were 5.42 grams for the right, and 5.05 grams for the left with room temperature 22.9 C. Immersion of the left hand in warm water reduced the flow in the right (for the first five minutes) to 4.01 grams per 100 c.c. per minute. For the remaining nine minutes of the period of immersion, the flow in the right hand rose to 6.16 grams per 100 c.c. per minute. A subsequent immersion of the left hand in cold water caused a diminution in the flow in the right to 3.26 grams but only for a single minute, the flow then rising for the remainder of the period of immersion to 5.3 grams per 100 c.c. per minute.

Gabriel M., a barber, aged 41, was admitted to Lakeside Hospital, November 13, with the diagnosis of tabes. He complains of seeing double, that the left leg is weaker than the right and that he gets tired in walking. The patellar and Achilles reflexes are absent from both sides. The biceps and triceps reflexes are present in both arms. The plantar reflex is normal. There is marked hypotonus of the iliofemoral muscles with ataxia. There is ataxia also of the toes. Vibration is everywhere perceived. Hypesthesia to the needle is noted in both lower extremities, with great delay in transmission. Over the left leg the delay is fully two seconds. Romberg's sign is positive. The spinal fluid is clear under normal pressure, the cell count 8, Noguchi negative, Wassermann strongly positive. The grip of the hands is fairly strong. There is no incoordination of the hand movements. Sometimes a good deal of pain is present in the legs especially at night. The feet are habitually cold. Particulars of the first examination of the blood flow in the hands on November 17 are given in the general table.

Second examination of blood flow in Gabriel M., November 19: Hands in bath at 3:43 p. m., in the calorimeters at 3:52. At 4:10 p. m. the left hand was put into water at 43 C. At 4:20 p. m. the right hand was taken out of the calorimeter. Pulse 100.

TABLE 18.—Calorimetric Measurements in Second Examination of Gabriel M.

Time	Right	Left	Room	Time	Right	Left	Room
3:51	31.73	31.64		4:07	31.75	31.65	24.15
3:53	31.72	31.63	24.0	4:08	31.755	31.655	
3:54	31.715	31.625	24.0	4:09	31.76	31.66	24.2
3:55	31.71	31.62		4:10	31.765	31.66	
3:56	31.71	31.62	24.0	4:11	31.77		
3:57	31.705	31.61		4:12	31.77	.....	24.2
3:58	31.71	31.62	24.1	4:13	31.78		
3:59	31.715	31.63		4:14	31.78	.....	24.2
4:00	31.72	31.635	24.1	4:15	31.79		
4:01	31.72	31.63		4:16	31.795	.....	24.3
4:02	31.72	31.63	24.1	4:17	31.795		
4:03	31.725	31.635		4:18	31.795	.....	24.4
4:04	31.73	31.64		4:19	31.80	.....	24.3
4:05	31.735	31.645	24.2	4:20	31.81		
4:06	31.74	31.65		4:33	31.65		

Cooling of hand calorimeters, R., 0.16 C. in thirteen minutes, L., 0.29 C. in twenty-three minutes. Volume of right hand, 424 c.c., of left 407 c.c. Water equivalent of calorimeters with contents, R., 3,434, L., 3,420. Rectal temperature 37.20 C.

Third examination of blood flow in Gabriel M., November 24. Feet in bath at 2:45 p. m., in calorimeters at 2:56. At 3:44 right foot put into water at 43 C. At 3:58 right foot put into water at 8.7 C. He felt it very cold at first. At 4:12 p. m. left foot taken out of calorimeter.

TABLE 19.—Calorimetric Measurements in Third Examination of Gabriel M.

Time	Right	Left	Room	Time	Right	Left	Room
2:55	31.82	31.86	20.1	3:38	30.88	30.94	22.3
2:58	31.63	31.66		3:40	30.87	30.93	
3:00	31.54	31.57		3:42	30.87	30.92	
3:02	31.47	31.52	20.3	3:44	30.86	30.90	
3:04	31.39	31.45	20.7	3:46	30.795	30.885	22.4
3:06	31.32	31.39	20.8	3:48	.....	30.87	22.5
3:08	31.26	31.35	21.0	3:50	.....	30.865	22.6
3:10	31.21	31.29	21.0	3:52	.....	30.86	22.6
3:12	31.17	31.25	21.1	3:54	.....	30.855	22.6
3:14	31.12	31.20	21.2	3:56	.....	30.85	22.7
3:16	31.08	31.16	21.3	3:58	.....	30.845	
3:18	31.05	31.13	21.4	4:00	.....	30.835	22.8
3:20	31.01	31.10	21.5	4:02	.....	30.83	22.8
3:22	30.98	31.07	21.7	4:04	.....	30.82	
3:24	30.96	31.05	21.7	4:06	.....	30.81	22.9
3:26	30.94	31.03	21.9	4:08	.....	30.80	23.1
3:28	30.92	31.01	22.0	4:10	.....	30.79	22.9
3:30	30.90	30.985		4:12	.....	30.77	
3:32	30.895	30.97	22.1	4:13	.....	30.755	
3:34	30.89	30.955	22.2	4:27	30.09	30.52	
3:36	30.88	30.95	22.2				

Cooling of foot calorimeters, R., 0.705 C. in forty-one minutes, L., 0.235 C. in fourteen minutes. Volume of right foot 1,092 c.c., of left 1,087 c.c. Water equivalent of foot calorimeters with contents R., 3,783, L., 3,779. Pulse 108.

Hands in bath at 4.33½ p. m., in calorimeters at 4:32, out of calorimeters at 4:43.

TABLE 20.—Calorimetric Measurements in Third Examination of Gabriel M.

Time	Right	Left	Room	Time	Right	Left	Room
4:31	31.48	31.39	24.2	4:39	31.41	31.355	
4:33	31.42	31.36	24.7	4:40	31.41	31.255	23.4
4:34	31.42	31.36	24.5	4:41	31.41	31.365	
4:35	31.415	31.355	24.2	4:42	31.41	31.365	
4:36	31.42	31.36		4:43	31.42	31.37	23.9
4:37	31.42	31.36	23.7	4:49	31.32	31.28	
4:38	31.41	31.36	23.4				

Cooling of hand calorimeters in six minutes, R., 0.10 C., L., 0.09 C. Rectal temperature 37.55 C. Volume of right hand 425 c.c., of left 390 c.c. Water equivalent of hand calorimeters with contents, R., 3,435, L., 3,407.

The flow in the right hand of Gabriel M. at the first examination was 1.0 gram, in the left 1.37 grams per 100 c.c. per minute with room temperature 22.6 C. Two days later the flows were 2.91 grams and 2.86 grams for the right and left hands respectively with the higher room temperature of 23.9 C. Immersion of the left hand in warm water caused scarcely any increase of flow in the right hand, which came out 3.07 grams per 100 c.c. per minute during the ten minutes of the period of immersion. The flow in the right foot at the same examination was 0.56 gram, and in the left 0.62 gram. The ratio of the combined foot flows to the combined hand flows was 1:4.89, indicating a relatively greater deficiency in the feet than in the hands. This is characteristic of all the cases of tabes examined. For a period

of twenty-two minutes immersion of the right foot in warm water the flow in the left foot was slightly increased (to 0.89 gram per 100 c.c. per minute).

At the third examination the flow in the right hand of Gabriel M. was 2.77 grams and in the left hand 2.88 grams with room temperature 22.1 C. The flow in the right foot before testing of the vasomotor reflexes was 0.96 gram and in the left foot 0.73 gram. The ratio of the combined foot to the combined hand flows was 1:3.93. During immersion of the right foot in warm water the flow in the left foot (for the first four minutes of the immersion) sank to 0.65 gram, and then rose to 0.92 gram per 100 c.c. per minute for the remaining ten minutes of the immersion period. When the right foot was subsequently put into cold water the change was slight, the flow in the left foot being 0.84 gram per 100 c.c. per minute for the first four minutes of the immersion and 0.70 gram for the remaining ten minutes.

TABLE 21.—Calorimetric Measurements in Second Examination of John M.

Time	Right	Left	Room	Time	Right	Left	Room
2:14	31.79	31.68		2:31	32.115	.....	24.4
2:15	31.77	31.67		2:32	32.15		
2:16	31.78	31.68	23.8	2:33	32.185	...	24.7
2:17	31.785	31.69		2:34	32.21		
2:18	31.795	31.70		2:35	32.24		
2:19	31.82	31.73	24.4	2:36	32.28		
2:20	31.85	31.76	24.2	2:37	32.31	.....	24.8
2:21	31.88	31.79		2:38	32.335		
2:22	31.90	31.82		2:39	32.37	.....	24.5
2:23	31.92	31.85		2:40	32.395		
2:24	31.94	31.87	23.9	2:41	32.42	.....	24.0
2:25	31.98	31.90		2:42	32.45		
2:26	32.00	31.93		2:43	32.49	.....	23.4
2:27	32.025	.....	24.1	2:44	32.52	.....	23.4
2:28	32.05			2:45	32.57	.....	23.8
2:29	32.07	.....	24.2	2:52	32.47	31.55	
2:30	32.09						

Cooling of hand calorimeters, R., 0.10 C. in seven minutes, L., 0.38 C. in twenty-six minutes. Volume of right hand 426 c.c., of left 399 c.c. Water equivalent of hand calorimeters with contents, R., 3,436, L., 3,414. Pulse 96.

John M., a laborer, aged 45, was admitted December 2 at Lakeside Hospital with the diagnosis of tabes, complaining of incontinence of urine and trouble in walking. A history was given of gonorrhea. He says he was bit in the arm twenty-eight years ago by a person supposed to have had lues. He denies having had chancre. His present illness seems to have commenced fourteen years ago. The reflexes are hypo-active in the biceps and supinator of both arms. The lower extremities are ataxic. The patellar and ankle reflexes are absent, also the plantar reflexes. There is no Babinski or Kernig's sign. Romberg's sign is positive. He feels a point on the feet but the response is slow. He walks fairly well, better than some time ago, he says. The pupils are equal, central and regular, but do not react to light and very sluggishly to accommodation. The skin of the nose is covered entirely by scar tissue; the septum is deficient posteriorly. Blood examination, erythrocytes 4,976,000, white blood corpuscles 6,200, hemoglobin 80 per cent. The blood flow was examined on

December 3 and December 8. The particulars of the flow in the feet at first examination of John M. are given in the general table.

Second examination of blood flow in John M., Dec. 8, 1914. Hands were in bath at 2:05 p. m., in calorimeters at 2:14½. At 2:26 p. m. the left hand was put into water at 8 C. At 2:36 p. m. the left hand was put into water at 43.1 C. At 2:45 p. m. the right hand was taken out of the calorimeter.

The feet were in bath at 2:55 p. m., in calorimeters at 3:06. At 3:41 p. m. right foot was put into water at 8.3 C. He feels it pretty cold. At 3:55 p. m. left foot taken out of calorimeter.

TABLE 22.—Calorimetric Measurements in Second Examination of John M. (Feet)

Time	Right	Left	Room	Time	Right	Left	Room
3:05	32.28	32.33	24.8	3:33	31.98	32.055	24.8
3:08	32.18	32.25	24.8	3:35	31.98	32.055	24.8
3:09	32.15	32.20	24.9	3:37	31.97	32.06	24.8
3:11	32.12	32.17		3:39	31.97	32.06	
3:13	32.11	32.16	24.5	3:41	31.96	32.065	24.8
3:15	32.10	32.155		3:43	31.88	32.065	24.7
3:17	32.09	32.145	24.8	3:45	.....	32.06	24.8
3:19	32.07	32.13	24.9	3:47	.....	32.055	
3:21	32.05	32.11	24.7	3:49	.....	32.05	24.5
3:23	32.02	32.085		3:51	.....	32.045	24.6
3:25	32.00	32.07	24.5	3:53	.....	32.04	24.8
3:27	32.00	32.065		3:55	.....	32.04	
3:29	31.99	32.06	24.5	3:58	.....	31.97	
3:31	31.985	32.06	24.7	4:04	31.51	31.86	

Cooling of foot calorimeters, R., 0.37 C. in twenty-one minutes, L., 0.11 C. in six minutes. Rectal temperature, 37.65 C. Volume of right foot, 1,006 c.c., of left, 1,001 c.c. Water equivalent of foot calorimeters with contents, R., 3,720, L., 3,716.

In John M. at the first examination the flows in the right and left foot respectively, before the vasomotor reflexes were tested, were 1.27 grams and 1.28 grams per 100 c.c. per minute, with room temperature 24.2 C. For a period of twelve minutes immersion of the right foot in cold water, the flow in the left was reduced to 0.95 gram per 100 c.c. per minute. Subsequent immersion of the right foot in warm water for a period of fourteen minutes caused an increase of the flow in the left to 1.52 grams per 100 c.c. per minute. Five days later the flow in the right hand was found to be 6.60 grams and in the left 7.57 grams with room temperature 24 C. When the left hand was put into cold water the flow in the right fell to 6.46 grams per 100 c.c. per minute for the first five minutes and then rose for the remaining five minutes of the period of immersion of the left hand, to 8.47 grams per 100 c.c. per minute, an insignificant reaction. When the left hand was subsequently immersed in warm water the flow in the right hand was only increased to 8.79 grams per 100 c.c. per minute for the whole nine minutes of the period of immersion. At the same examination the flow in the right foot came out, before the vasomotor reflexes were tested, 1.35 grams per 100 c.c. per minute and that in the left foot 1.57 grams, with room temperature 24.7 C. The ratio of the combined foot flow to the combined hand flow was 1:4.85. The room was warm and the

patient perspiring, so that the flows both in hands and feet are really more deficient than the actual numbers would suggest, and the same is true for the foot flows at the first examination. When the right foot was immersed in cold water the flow in the left foot was only slightly changed, falling to 1.39 grams per 100 c.c. per minute for the whole fourteen minutes of the immersion.

The case of Joseph K. is of interest, inasmuch as the suggested diagnosis of malingering was not, as regards the symptoms described in the legs, supported by the blood flow examination, which, on the contrary, indicated a real pathologic condition.

Joseph K., a laborer, aged 48, was admitted to the hospital June 17. There appears to be delayed sensation in the extremities. He says that he does not feel heat or vibratory sensation in the thighs. Pin pricks are apparently not well recognized. Knee-jerk and Achilles reflex are strong. He complains of pain in the left leg. Says he has cold sweats on legs and feet at night in bed. His legs feel cold to his hand, although he expects them to be warm since they are covered with sweat. He pinches his calf and says he feels nothing there. A zone on the calves is apparently anesthetic to contact. In front on the shins

TABLE 23.—Calorimetric Measurements in Case of Joseph K.

Time	Right	Left	Room	Time	Right	Left	Room
1:53	31.13	31.12		2:12	31.905		
1:55	31.12	31.125	27.2	2:13	31.925	.....	27.4
1:56	31.16	31.16		2:14	31.96		
1:57	31.21	31.22		2:15	31.995		
1:58	31.26	31.27	27.2	2:16	32.025	.....	27.4
1:59	31.31	31.325		2:17	32.05		
2:00	31.36	31.36		2:18	32.08		
2:01	31.42	31.41	27.3	2:19	32.12	.....	27.5
2:02	31.49	31.47		2:20	32.165		
2:03	31.54	31.525		2:21	32.205		
2:04	31.605	31.585	27.3	2:22	32.26		
2:05	31.68	31.64		2:23	32.30	.....	27.55
2:06	31.73	31.60		2:24	32.365		
2:07	31.76			2:25	32.42		
2:08	31.79	.....	27.3	2:26	32.48	.....	27.55
2:09	31.80			2:27	32.545		
2:10	31.825			2:33	32.49	31.505	
2:11	31.87						

Cooling of calorimeters, R., 0.055 C. in six minutes, L., 0.195 C. in twenty-seven minutes. Volume of right hand 495 c.c., of left hand 479 c.c. Water equivalent of calorimeters with contents, R., 3,491, L., 3,478. Rectal temperature 37.55 C.

at this level he feels contact, as also on the patellae and on the feet. He feels warm water on the feet. He says his hand "shortens" when he tries to write. His pupils react to light and accommodation. The chest examination reveals nothing special. Temperature normal. Blood examination on June 24 gave erythrocytes 5,120,000; leukocytes 9,400; hemoglobin 85 per cent. Two Wassermann tests were negative for blood, as also the Wassermann and Noguchi reactions for spinal fluid. On June 26 pin pricks were better appreciated over the thighs; the knee-jerks were not strong, but were equal on the two sides. The patient was discharged on July 3 "cured," with a suggestion that he was malingering. Blood flow in the hands and feet was examined on June 26. The day was warm.

Hands in bath at 1:41 p. m., in calorimeters at 1:54⅓ p. m. At 2:06 p. m. left hand immersed in cold water (8.5 C.). He says he feels the water very

cold. At 2:16 p. m. left hand put into water at 41.4 C. At 2:27 the right hand taken out of calorimeter.

The flow in the right hand in Joseph K. was 8.94 grams and in the left 8.75 grams per 100 c.c. per minute with room temperature 27.3 C. For the man's age and the high room temperature, these flows are fair but by no means large, and the slight preponderance in the right hand is entirely normal. The vasomotor reflexes in the hand both to cold and warmth were also normal in intensity and duration. In the feet, on the contrary, the flows came out extremely small, especially taking into account the high room temperature (0.50 grams for the right and 0.54 gram per 100 c.c. per minute for the left foot, with room temperature 26.4 C.). This is quite in agreement with the patient's statement as to the coldness of his feet. Also there was total absence of any vasomotor reflex in the left foot when the right was immersed for ten minutes in warm water, the flow remaining unchanged (0.53 gram). While the patient might have showed some temporary improvement in his not very obtrusive symptoms during his stay in the hospital, it seems unlikely that such definite blood flow results for the feet should be devoid of significance. They at any rate would suggest the necessity in such a case of renewed careful examination of the patient before the suggestion of malingering could be accepted.

In Fred L., a man aged 22, with a glioma of the occipital lobe, the striking feature of the blood-flow examination was the great intensity of the contralateral vasomotor reflexes both to heat and cold. Two examinations were made within eight days and this was clearly seen at both. It is a plausible suggestion that the increased intracranial pressure, of which there were evident symptoms, may have rendered the vasomotor centers hyperexcitable. It is possible also that the rather small flows for the age of the patient might have been due to a peripheral vasoconstriction produced in this way in the interest of the brain circulation.

Fred. L. was first admitted to Lakeside Hospital, June 30, 1908. He complained of dizzy attacks and severe headache. The attacks occurred about once a week and varied in intensity. There was never any nausea or vomiting. Severe headaches had occurred nearly every day since his first trouble. Examination of the eyes showed choked disk and hemianopsia. He could not see objects at his right. Hearing, the same on both sides, was a little less acute than normal. Numerous lumbar punctures were made, and finally a decompression operation was done. Two years later he reported to the dispensary much improved. He again reported July 18, 1911, that occipital headache came on at night and prevented sleep. Only large doses of morphin quieted him at all. He was readmitted to the hospital, Oct. 8, 1912. Hemianopsia was present as before. The blood flow in the hands was twice examined (Nov. 18 and Nov. 26, 1912). On November 27 he left the hospital for Thanksgiving and returned on November 28 with severe headache and vomiting. On November 29 an operation was resolved on, during which he died. The necropsy showed a

glioma with cystic degeneration in the left occipital lobe resting on the tentorium. The cyst measured about 5 cm. by 3 cm.

First blood flow examination of Fred. L.: Hands in bath at 3:07 p. m., in calorimeters at 3:20½. At 3:38 left hand immersed in water at 43 C. Pulse 88. At 3:50 p. m. the left hand was put into water at 11.2 C. He feels the water very cold. At 4:02 right hand was removed from calorimeter.

TABLE 24.—Calorimetric Measurements in Case of Fred. L.

Time	Right	Left	Room
3:20	30.44	30.42	
3:22	30.37	30.40	
3:23	30.38	30.41	
3:24	30.38	30.42	
3:25	30.385	30.43	22.0
3:26	30.41	30.47	
3:27	30.43	30.50	22.1
3:28	30.48	30.53	
3:29	30.52	30.565	22.1
3:30	30.58	30.58	
3:31	30.60	30.60	22.0
3:32	30.61	30.62	
3:33	30.63	30.64	22.0
3:34	30.66	30.68	
3:35	30.69	30.70	
3:36	30.71	30.71*	
3:37	30.71	30.71	
3:38	30.73	30.70	
3:39	30.74		
3:40	30.765		
3:41	30.80		
3:42	30.83		
3:43	30.88		
3:44	30.92		
3:45	30.96		
3:46	31.01		
3:47	31.06		
3:48	31.09	30.58	
3:49	31.12		
3:50	31.18		
3:51	31.18		
3:52	31.185		
3:53	31.19		
3:54	31.19	.....	23.0
3:55	31.19		
3:56	31.195	.....	22.8
3:57	31.225		
3:58	31.245	.....	22.5
3:59	31.25	.....	22.1
4:00	31.27		
4:01	31.28	.....	22.2
4:02	31.31		
4:12	31.19		

Cooling of calorimeters in ten minutes, R., 0.12 C., L., 0.11 C. Volume of right hand 385 c.c., of left 377 c.c. His hands are thin. Water equivalent of calorimeters with contents, R., 3,403, L., 3,397. Rectal temperature 37.7 C.

* He is paying great attention to the preparations for the warm water test.

TABLE 25.—Calorimetric Measurements in Second Examination of Fred. L.

Time	Right	Left	Room
10:57½	31.17	31.19	21.0
11:00	31.195	31.21	
11:01	31.205	31.225	
11:02	31.21	31.26	21.5
11:03	31.22	31.28	
11:04	31.24	31.295	21.5
11:05	31.295	31.31	
11:06	31.295	31.335	21.4
11:07	31.32	31.35	
11:08	31.34	31.37	21.35
11:09	31.39	31.395	
11:10	31.395	31.405	
11:11	31.42	31.42	
11:12	31.45	31.435	
11:13	31.50	31.46	
11:14	.....	31.465	20.9
11:15	.....	31.48	
11:16	.....	31.505	
11:17	.....	31.555	20.7
11:18	.....	31.605	
11:19	.....	31.635	20.7
11:20	.....	31.675	
11:21	.....	31.69	
11:22	.....	31.73	20.6
11:23	.....	31.76	
11:24	.....	31.785	20.6
11:25	.....	31.795	
11:26	.....	31.80	20.7
11:27	.....	31.795	
11:28	.....	31.80	
11:29	.....	31.805	20.7
11:30	.....	31.81	
11:31	.....	31.82	
11:32	.....	31.82	
11:33	.....	31.82	20.7
11:34	.....	31.815	
11:35	.....	31.825	
11:36	.....	31.835	
11:37	.....	31.86	20.7
11:38	.....	31.875	
11:39	.....	31.89	20.7
11:40	.....	31.90	
11:41	.....	31.915	
11:42	.....	31.935	
11:43	.....	31.95	20.7
11:44	.....	31.965	
11:45	.....	31.975	
11:46	.....	31.99	
12:02	30.82	31.725	

Cooling of calorimeters, R., 0.68 C. in 49 minutes, L., 0.265 C. in sixteen minutes. Volume of right hand 389 c.c., of left 380 c.c. Water equivalent of calorimeters with contents, R., 3,406, L., 3,399. Rectal temperature 37.75 C.

Second blood flow examination of Fred. L.: He says he is feeling better than at the previous examination though he was sick (vomiting) all yesterday morning. Hands were in bath at 10:45½ a. m., in calorimeters at 10:58½. At 11:13 a. m. the right hand was put into water at 43 C. At 11:24 a. m. the right hand was put into water at 10.5 C. At 11:35 right hand was again immersed in water at 43 C. At 11:46 right hand was taken out of calorimeter. Pulse 100.

At the first examination the flow in the right hand in Fred L. was 5.43 grams and in the left 4.80 grams per 100 c.c. per minute with room temperature 22 C. (ratio 1:1.13). Immersion of the left hand in warm water reduced the flow for the first two minutes in the right hand to 4.18 grams per 100 c.c. per minute. For the remaining ten minutes of the period of immersion the flow in the right hand rose to 8.28 grams per 100 c.c. per minute, a marked reflex vasodilatation. When the left hand was now immersed in cold water the flow in the right hand fell to 2.28 grams per 100 c.c. per minute for the first six minutes of the period of immersion. For the remaining six minutes of the period it rose somewhat but only to 4.84 grams. The reflex vasoconstriction was thus very intense and durable. At the second examination the flow for the right hand, before the vasomotor reaction was tested, was 6.15 grams per 100 c.c. per minute and for the left 5.49 grams with room temperature 21.4 C. (ratio 1:1.12, almost precisely the same as at the previous examination). The vasomotor reflex tests also showed intense and persistent effects.

In a young man (J. S.), recovering from tetanus after antitoxin treatment, vasomotor reflexes fully as intense were observed. There was no direct evidence that this condition was due to the action of the tetanus toxin or antitoxin on the nervous system, but the extent of the crossed vasomotor reflexes was certainly notable.

TABLE 26.—Calorimetric Measurements in Case of J. S.

Time	Right	Left	Room	Time	Right	Left	Room
1:37	30.53	30.54		1:54	30.74		
1:39	30.49	30.51	25.5	1:55	30.795		
1:40	30.48	30.49		1:56	30.83		
1:41	30.47	30.49		1:57	30.89		
1:42	30.48	30.50		1:58	30.935	.....	26.0
1:43	30.495	30.52		1:59	30.995		
1:44	30.51	30.54	26.0	2:00	31.05		
1:45	30.535	30.56		2:01	31.08		
1:46	30.58	30.61		2:02	31.095		
1:47	30.61	30.64		2:03	31.10	.....	26.0
1:48	30.63	30.67	25.9	2:04	31.16		
1:49	30.65	30.72		2:05	31.22		
1:50	30.68	30.74		2:06	31.27	.....	25.8
1:51	30.69			2:07	31.31		
1:52	30.705	.....	26.2	2:08	31.37		
1:53	30.72			2:17	31.29	30.55	

Cooling of calorimeters, R., 0.08 C. in nine minutes, L., 0.19 C. in twenty-seven minutes. Volume of right hand 389 c.c., of left hand 358 c.c.

J. S., a young laborer, was admitted to the City Hospital, March 18, suffering from tetanus. On March 9 his right thumb was injured by a machine. On March 16 pain and stiffness were present in the jaw. Three days later his back

was stiff and painful; attacks of cramp-like rigidity occurred. When admitted there was a spastic condition of legs, arms and hands, and some spasm of the jaw. He was treated with large doses of antitoxin. The blood flow in the hands was examined on April 5. The thumb had nearly healed. The knee-jerks were still exaggerated.

The hands were in bath at 1:28 p. m., in calorimeters at 1:38. At 1:50 p. m. the left hand was immersed in water at 43.5 C. At 2:00 p. m. the left hand was put into water at 7 C. At 2:08 p. m. the right hand was taken out of the calorimeter. Pulse 92, rather weak. Mouth temperature 37.3 C.

The initial flow in the hands of J. S. was subnormal for his age and the room temperature (5.32 grams per 100 c.c. per minute for the right hand and 6.3 grams for the left, with room temperature 25.9 C.). On immersion of the left hand in warm water the flow in the right fell to 3.32 grams per 100 c.c. per minute for the first four minutes and then rose to 9.09 grams for the remaining six minutes of the immersion. When the left hand was now put into cold water the flow in the right was cut down to 3.9 grams per 100 c.c. per minute for the first three minutes and then increased (for the remaining five minutes) to 10.14 grams per 100 c.c. per minute. The vasomotor reaction to cold accordingly, although initially intense, was not especially persistent, giving way to a marked vasodilatation while the contralateral hand was still in the cold water.

The effect of certain poisons on the vasomotor reflexes, as investigated by this method, seemed sufficiently definite to be worthy of mention.

TABLE 27.—Calorimetric Measurements in Case of Mrs. X.

Time	Right	Left	Room
3:07	29.965	29.97	
3:09	29.995	30.03	27.2
3:10	30.03	30.07	
3:11	30.09	30.13	
3:12	30.16	30.205	
3:13	30.25	30.26	
3:14	30.33	30.34	
3:15	30.45	30.45	27.3
3:16	30.525	30.53	
3:17	30.605	30.625	
3:18	30.68	30.68	
3:19	30.72	30.73*	
3:20	30.755	30.755	
3:21	30.795	30.79	
3:22	.....	30.805	
3:23	.....	30.82	
3:24	.....	30.85	
3:25	.....	30.925	27.3
3:26	.....	30.99	
3:27	.....	31.03	
3:28	.....	31.11	
3:29	.....	31.155	
3:30	.....	31.20	
3:31	.....	31.24	
3:32	.....	31.27	
3:33	.....	31.33	27.4
3:34	.....	31.42	
3:35	.....	31.50	
3:36	.....	31.60	
3:37	.....	31.655	
3:38	.....	31.71	
3:38½	.....	31.74	
3:48	30.625	.....	27.3
3:48½	.....	31.675	

*Here she began to get nervous about the cold water which she saw in preparation being cooled by ice.

Cooling of calorimeters, R., 0.17 C. in twenty-seven minutes, L., 0.065 C. in ten minutes. Volume of right hand 317 c.c., of left hand 326 c.c.

Mrs. X., aged 48, height 4 feet, 10 inches, weight 118 pounds, was admitted at the dispensary May 11, 1911, complaining of a cough that she had had for a week. Her general health was undisturbed. She had had no children but

eight miscarriages. She was obviously under the influence of alcohol, and for this reason the blood flow in the hands was examined.

The hands were in bath at 2:59 p. m., in calorimeters at 3:08. At 3:21 the right hand was put into water at 8.4 C. At 3:30 the right hand was put into water at 43 C. At 3:38½ the left hand was taken out of the calorimeter. Mouth temperature 37.35 C. Pulse 96.

The initial flow in this case was good (13.05 grams per 100 c.c. per minute for the right hand and 12.03 grams for the left), even for the relatively high room temperature (27.3 C.). The flow in the left hand was diminished to 4.6 grams when the right was immersed in cold water. After three minutes the vasoconstriction gave place to vasodilatation, the flow increasing to 11.08 grams for the remaining six minutes of immersion of the right hand in cold water. On immersing the right hand in warm water the flow in the left sank to 7.52 grams per 100 c.c. per minute (for three minutes) and then increased to 15.92 grams per 100 c.c. per minute for the remaining five and one-half minutes of immersion, an exceptionally large increase on the top of the good initial flow. The suggestion is that the influence of the alcohol favors reflex vasodilatation of the cutaneous vessels. Evidence of this has also been secured in other cases.

In a case of lead poisoning with no symptoms of peripheral neuritis (John K.) the opposite result was obtained, good crossed vasoconstriction but practically no increase of the initial flow. In other words, the vasomotor mechanism, which under the influence of alcohol was exceptionally ready to respond to appropriate stimuli by vasodilatation, tended, under the influence of lead poisoning, to respond especially to stimuli causing vasoconstriction. In accordance with this the blood pressure was high in John K. (180 mm. Hg). There was no decided anemia and the flow in the hands before the vasomotor reactions were tested was within the normal range (8.96 grams per 100 c.c. per minute for the right hand and 8.81 grams for the left, with room temperature 23 C.).

John K., a laborer, aged 52, was admitted to the City Hospital, May 13. He worked in an automobile factory scraping paint from wheels. For two weeks he had been constipated, with intense pain in the abdomen and the occurrence of vomiting. A lead line was noted on the gums. The lips were red. A blood count showed erythrocytes 4,080,000, leukocytes 6,800. Knee-jerks were present and equal. The grip of the hands was not noticeably weakened. The pupils reacted to light and accommodation. The radial pulse was regular and of high tension. There was some fibrosis of the artery. He was discharged improved on May 25. The blood flow in the hands was examined May 14. He works best with his left hand though he eats and writes with the right.

The hands were in bath at 1:43 p. m., in calorimeters at 1:55½. At 2:09 the left hand was put into water at 8 C. At 2:20 the left hand was put into water at 43.2 C. At 2:33 the right hand was taken out of the calorimeter.

TABLE 28.—Calorimetric Measurements in Case of John K.

Time	Right	Left	Room	Time	Right	Left	Room
1:55	31.00	30.87		2:16	31.895		
1:57	31.07	30.94		2:17	31.925	.....	22.3
1:58	31.12	31.00		2:18	31.97		
2:00	31.21	31.08		2:19	31.99		
2:01	31.27	31.15		2:20	32.02		
2:02	31.33	31.21	23.2	2:21	32.05		
2:03	31.39	31.27		2:22	32.075	.....	22.3
2:04	31.45	31.33		2:23	32.10		
2:05	31.50	31.39		2:24	32.125		
2:06	31.56	31.44	23.0	2:25	32.16		
2:07	31.62	31.50*		2:26	32.21		
2:08	31.65	31.53		2:27	32.25	.....	22.3
2:09	31.68	31.56		2:28	32.295		
2:10	31.71			2:29	32.32		
2:11	31.72			2:30	32.36		
2:12	31.735			2:31	32.395	.....	22.3
2:13	31.78	.....	22.4	2:32	32.435		
2:14	31.81			2:33	32.48	.....	22.4
2:15	31.87			2:46	32.29	31.10	

* Here he saw ice brought and put into the cold water and seemed to become apprehensive.

Cooling of calorimeters, R., 0.19 C. in thirteen minutes; L., 0.46 C. in thirty-seven minutes. Volume of right hand 475 c.c., of left 472 c.c. Water equivalent of calorimeters with contents, R., 3,475, L., 3,473. Pulse 108.

In another case of lead poisoning (S.), a man aged 40, the flow was 8.05 grams in the right and 8.74 grams in the left hand with room temperature 21.8 C. In this case also the tendency to reflex vasoconstriction was decided, as will be seen by referring to the general table of results.

TABLE 29.—Calorimetric Measurements in Case of S.

Time	Right	Left	Room	Time	Right	Left	Room
3:40	30.03	30.13		3:58	31.11		
3:41	30.10	30.20	21.9	3:59	31.12		
3:42	30.16	30.26		4:00	31.15		
3:43	30.20	30.32		4:01	31.17		
3:44	30.28	30.39		4:02	31.18	.....	21.7
3:45	30.335	30.45	21.8	4:03	31.195		
3:46	30.40	30.53		4:04	31.26		
3:47	30.495	30.625		4:05	31.31		
3:48	30.58	30.71		4:06	31.375	.....	22.9
3:49	30.63	30.79		4:07	31.42		
3:50	30.66			4:08	31.47		
3:51	30.69			4:10	31.53		
3:52	30.72			4:11	31.57		
3:53	30.78	.....	21.9	4:12	31.60	.....	22.8
3:54	30.86			4:13	31.64		
3:55	30.91			4:14	31.695		
3:56	31.00			4:27	31.53	30.37	22.5
3:57	31.07	.....	21.5				

Cooling of calorimeters, R., 0.165 C. in thirteen minutes, L., 0.42 C. in thirty-eight minutes. Volume of right hand 527 c.c., of left hand 521 c.c. Rectal temperature 38.05 C.

S., a painter, aged 40, height 5 feet, 8½ inches, was admitted to the City Hospital, March 31. He complained of colic, and a blue line was noted around his gums. He had been ill two or three months, and although weak was considerably better. He had no wrist-drop. He was discharged improved April 15. The blood flow in the hands was examined on April 3. Hands were in bath at 3:29 p. m., in calorimeters at 3:39. At 3:49 the left hand was put in water

at 8 C. He felt it very cold. At 4:01 p. m. the left hand was put into water at 43 C. At 4:09 left hand dried and wrapped. At 4:14 the right hand was taken out of calorimeter. Pulse 120.

In Roderick D., a blacksmith, aged 27, excessively addicted to cigaret smoking from boyhood, the flow in the hands was large (12.77 grams for the right and 12.38 grams for the left hand per 100 c.c. per minute, with the rather high room temperature of 26.2 C.). Immersion of the left hand in cold water caused a transient vasoconstriction of the right, the flow falling to 7.73 grams for the first two minutes of immersion, to rise again to 11.03 grams per 100 c.c. per minute for the remaining nine minutes, during which the left hand continued in the cold water. Warm water caused only a small preliminary vasoconstriction, the flow then increasing again though not quite to the high initial value. Scratching the skin with a blunt point caused a well-marked red line which persisted for a considerable time. In this case everything points to the existence of a tendency to vasodilatation, which is in agreement with the observation that nicotin after a preliminary excitation causes depression of the sympathetic nerve cells.

Examination of flow in hands of Roderick D.: Hands in bath at 2:35½ p. m., in calorimeters at 2:47¼. At 2:59 the left hand was put into water at 8 C. He felt it very cold. At 3:10⅛ p. m. the left hand was put into water at 43.5 C. At 3:21 right hand was taken out of calorimeter.

TABLE 30.—Calorimetric Measurements in Case of Roderick D.

Time	Right	Left	Room	Time	Right	Left	Room
2:46½	29.88	29.84		3:06	31.70		
2:48	29.96	29.91		3:07	31.76		
2:49	30.07	30.04	26.2	3:08	31.83		
2:50	30.19	30.20		3:09	31.90	.....	26.3
2:51	30.30	30.31		3:10	31.99		
2:52	30.435	30.44	26.15	3:11	32.06		
2:53	30.565	30.54		3:12	32.11		
2:54	30.65	30.61		3:13	32.17		
2:55	30.78	30.72	26.2	3:14	32.20		
2:56	30.87	30.81		3:15	32.27		
2:57	31.01	30.90		3:16	32.33		
2:58	31.09	30.98	26.3	3:17	32.39		
2:59	31.19	31.065		3:18	32.46	.....	26.4
3:00	31.24			3:19	32.52		
3:01	31.30			3:20	32.56		
3:02	31.37			3:21	32.63	.....	26.5
3:03	31.46			3:22	.....	30.89	
3:04	31.56	.....	26.4	3:34	32.50		
3:05	31.63						

Cooling of calorimeters, R., 0.13 C. in thirteen minutes, L., 0.175 C. in twenty-three minutes. Volume of right hand 535 c.c., of left hand 513 c.c. Water equivalent of calorimeters with contents, R., 3,523, L., 3,505. Mouth temperature 37.4. Pulse 84.

The last case to be cited is that of a young man who shot himself through the brain.

Andrew K., a young foreign laborer, was brought to the City Hospital by the police on May 16, at 4:45 p. m., with a crescent-shaped wound in the scalp on the left side not far from the median line, midway between the glabella and

TABLE OF RESULTS OF CALORIMETRIC MEASUREMENTS IN TWENTY-ONE CASES *

Case	Age	Date	Pulse Rate	Temperature (C) of Room	Temperature (C) of Arterial Blood	Temperature (C) of Calorimeters Right	Temperature (C) of Calorimeters Left	Volume of Part in c.c. Right	Volume of Part in c.c. Left	Heat Given Off in Gm.-Calories Right	Heat Given Off in Gm.-Calories Left	Heat Given Off in Gm.-Calories In Mins.	Blood Flow in Gm. per Min. Right	Blood Flow in Gm. per Min. Left	Flow per 100 c.c. of Part per Min. Right	Flow per 100 c.c. of Part per Min. Left	Notes
Kaspar J. ...	50	5/ 5/11	92	24.2	36.70	29.79	29.66	511	457	1,121	830	8	22.54	16.38	4.80	3.58	Brachial neuritis (rt.). Hands.
				24.2	.....	30.05	.....	...	...	1,121	.....	7	26.76	.....	5.69	.....	Left hand in water at 43 C.
				24.4	.....	30.20	.....	...	...	210	.....	2	17.95	.....	3.82	.....	Left hand in water at 9.5 C.
				24.4	.....	30.33	.....	...	...	1,051	.....	7	26.19	.....	5.55	.....	Left hand still in cold water.
		5/ 8/11	57	25.3	36.70	30.20	30.34	523	478	1,511	1,426	14	18.45	17.79	3.76	3.72	Hands.
				25.4	.....	30.39	.....	...	...	299	.....	4	13.16	.....	2.68	.....	Left hand in water at 42.6 C.
				25.4	....	30.50	.....	...	...	790	.....	7	20.22	.....	4.12	.....	Left hand still in warm water.
				25.3	.....	30.60	.....	...	...	221	.....	3	13.44	.....	2.74	.....	Left hand in water at 8.2 C.
				25.3	....	30.69	.....	...	...	597	.....	6	18.40	.....	3.75	.....	Left hand still in cold water.
John McH	58	6/ 5/12	...	23.3	37.15	31.10	31.04	494	476	2,199	1,947	19	21.25	18.63	4.30	3.91	Hands.
		6/ 6/12	88	23.3	37.00	31.66	31.54	512	491	2,418	2,058	18	27.95	23.26	5.46	4.74	
				22.9	.....	31.91	.....	...	...	455	.....	6	16.55	.....	3.23	.....	Left hand in water at 43 C.
				23.0	.....	32.03	.....	...	...	981	.....	7	31.33	.....	6.11	.....	Left hand still in warm water.
Frank S.	64	4/23/12	96	21.0	36.70	29.46	29.35	1,020	950	210	414	14	2.30	4.47	0.22	0.47	Feet.
				21.3	.....	.....	29.16	....	...	.....	280	10	.....	4.12	.....	0.43	Right foot in water at 44 C.
				22.1	36.80	30.94	31.09	427	418	756	755	8	17.92	18.36	4.20	4.39	Hands.
		5/15/12	112	22.9	37.10	31.18	31.19	423	423	1,304	1,510	12	20.39	23.57	4.82	5.57	Hands.
Chas. deM.	28	7/10/12	68	30.1	37.00	31.85	31.88	488	479	3,380	3,565	15	48.61	51.57	9.96	10.76	Alcoholic neuritis. Hands.
		(Blood		29.9	.....	.....	32.41	...	...	.....	347	3	.....	28.00	.....	5.84	Right hand in water at 8.1 C.
		pressure,		29.8	.....	.....	32.61	...	...	.....	1,253	7	.....	45.30	.....	9.45	Right hand still in cold water.
		121.74)		29.8	.....	.....	32.81	...	...	.....	313	2	.....	41.50	.....	8.66	Right hand in water at 43.1 C.
				29.7	.....	.....	33.01	...	...	.....	1,357	7	.....	53.99	.....	11.27	Right hand still in warm water.
		7/16/12	84	25.1	37.20	31.73	31.67	479	494	2,574	2,303	11	47.53	42.06	9.92	8.95	Allowing for swelling left hand.
				24.0	37.10	30.91	31.02	1,437	1,452	1,581	2,097	22	12.90	17.40	0.90	1.20	Feet.
Frank D. ...	39	7/23/12	76	25.2	37.10	31.68	31.55	572	542	3,126	3,141	11	58.25	57.16	10.18	10.54	Left wrist drop (pressure).
		(Blood		25.1	.....	.....	32.01	...	...	.....	670	5	.....	29.25	.....	5.40	Right hand in water at 8 C.
		pressure,		25.1	.....	.....	32.14	...	...	.....	1,200	6	.....	44.80	.....	8.26	Right hand still in cold water.
		133.86)		25.2	.....	.....	32.38	...	...	.....	390	5	.....	18.36	.....	3.38	Right hand in water at 43 C.
				25.2	.....	.....	32.63	...	...	.....	1,886	8	.....	58.60	.....	10.81	Right hand still in warm water.
Stanislas C.	32	4/19/11	72	23.7	36.8	30.16	29.91	486	442	1,220	242	6	34.02	6.50	7.0	1.47	Hands.
				23.7	.....	30.46	.....	...	...	871	.....	4	38.17	.....	7.85	.....	Left hand in water at 12 C.
				23.6	.....	30.69	.....	...	...	766	.....	3	46.42	.....	9.55	.....	Left hand dried and wrapped.
				23.5	....	30.99	.....	...	...	1,568	.....	6	49.98	.....	10.28	.....	Left hand in water at 43.5 C.
				23.7	.....	31.39	.....	...	...	1,463	.....	6	50.08	.....	10.30	.....	Left hand in water at 9 C.
				23.5	.....	31.68	.....	...	...	731	.....	3	52.89	.....	10.88	.....	Left hand dried and wrapped.
Mrs. Eva M.	56	4/16/12	104	23.0	37.45	30.75	30.58	334	328	2,286	1,611	18	21.06	14.47	6.30	4.38	Left hemiplegia. Hands.
George H. .	40	7/18/12	68	26.5	36.95	31.76	31.96	461	500	1,889	2,604	12	33.70	49.10	7.26	9.82	Right hemiplegia. Hands.
		(Blood		26.7	.....	32.01	.....	...	...	312	....	3	23.39	.....	5.04	.....	Left hand in water at 8 C.
		pressure,		26.1	.....	32.17	.....	...	...	1,109	.....	7	36.82	.....	7.93	.....	Left hand still in cold water.
		91.83)		26.4	.....	32.41	.....	...	...	1,126	.....	10	27.55	.....	5.94	.....	Left hand in water at 43 C.
		7/25/12	86	25.5	36.90	31.65	31.83	455	497	2,421	3,597	12	42.70	65.69	9.38	13.21	Hands.
				24.7	.....	31.06	31.07	1,299	1,265	1,335	1,410	12	21.16	22.39	1.63	1.77	Feet.

* The tabular summary of results on A. O. H., Casimir M., John S., Mrs. M. C., Max B., Mrs. Mary N., C. and Abe K. is given in Table II, Heart, 1911, iii, 84.

Dennis H. ..	41	4/11/12 (Blood pressure, 118)	80	25.5	36.8	30.64	30.66	505	451	1,995	1,590	17	21.17	16.92	4.19	3.75	Left hemiplegia. Hands.
				25.5	.....	30.47	30.51	...	...	490	276	6	14.33	8.13	2.84	1.80	For the first six minutes.
				25.4	.....	.....	30.87	...	...	.....	588	7	.....	15.74	.....	3.49	Right hand in water at 8 C.
				25.4	.....	.....	31.03	...	...	.....	967	7	.....	26.60	.....	5.90	Right hand still in cold water.
				25.4	.....	.....	31.18	...	...	.....	484	4	.....	23.92	.....	5.30	Right hand in water at 43 C.
				25.4	.....	.....	31.33	...	...	.....	967	8	.....	24.55	.....	5.51	Right hand still in warm water.
Joseph S.	54	8/ 7/12	124	25.0	37.75	31.12	31.14	1,110	1,104	594	686	12	8.30	9.61	0.76	0.88	Feet. Tabes.
				25.0	37.85	31.43	31.30	425	441	1,872	1,465	13	24.92	19.11	5.86	4.33	Hands.
				25.0	.....	31.68	.....	...	...	492	.....	4	22.15	.....	5.21	.....	Left hand put in water at 8.4 C.
				25.0	.....	31.83	.....	...	...	1,002	.....	8	23.11	.....	5.43	.....	Left hand still in cold water.
				25.0	.....	32.00	.....	...	...	584	.....	5	22.18	.....	5.22	.....	Left hand in water at 42.8 C.
				25.2	.....	32.12	.....	...	...	721	.....	6	23.30	.....	5.48	.....	Left hand still in warm water.
W. B. C. ..	57	11/11/14	84	21.5	36.30	30.98	31.02	925	943	384	624	16	5.01	8.27	0.54	0.87	Feet. Tabes.
				21.8	.....	30.85	.....	...	...	413	.....	12	7.01	.....	0.75	.....	Left foot in water at 44.1 C.
				22.9	36.40	31.82	31.81	380	388	850	810	10	20.62	19.60	5.42	5.05	Hands.
				22.9	.....	31.88	.....	...	...	310	.....	5	15.24	.....	4.01	.....	Left hand in water at 44.5 C.
				22.8	.....	31.95	.....	...	...	845	.....	9	23.44	.....	6.16	.....	Left hand still in warm water.
				22.8	.....	32.01	.....	...	...	49	.....	1	12.40	.....	3.26	.....	Left hand in water at 13 C.
				22.6	.....	32.05	.....	...	...	631	.....	8	20.14	.....	5.30	.....	Left hand still in cold water.
Gabriel M. ..	41	11/17/14	92	22.6	36.76	31.50	31.50	431	395	390	491	19	4.33	5.44	1.00	1.37	Tabes. Hands.
		11/19/14	100	23.9	36.70	31.74	31.64	424	407	827	797	15	12.35	11.66	2.91	2.86	Hands.
				24.3	.....	31.79	.....	...	...	577	.....	10	13.05	.....	3.07	.....	Left hand in water at 43 C.
				22.8	36.60	31.18	31.12	1,117	1,092	369	404	12	6.30	6.82	0.56	0.62	Feet.
				23.0	.....	.....	30.99	...	...	.....	1,085	22	.....	9.76	.....	0.89	Right foot in water at 43.5 C.
		11/24/14	108	22.1	37.05	31.42	31.36	425	390	478	461	8	11.79	11.25	2.77	2.88	Hands.
				22.2	36.95	30.88	30.94	1,092	1,087	806	605	14	10.53	7.98	0.96	0.73	Feet.
				22.5	.....	.....	30.88	...	...	.....	155	4	.....	7.09	.....	0.65	Right foot in water at 43 C.
				22.6	.....	.....	30.86	...	...	.....	551	10	.....	10.05	.....	0.92	Right foot still in warm water.
				22.8	.....	.....	30.84	...	...	.....	202	4	.....	9.18	.....	0.84	Right foot in water at 8.7 C.
				23.0	.....	.....	30.80	...	...	.....	421	10	.....	7.60	.....	0.70	Right foot still in cold water.
John M. ...	45	12/ 3/14	116	24.2	37.05	31.46	31.52	1,067	1,042	960	936	14	13.62	13.43	1.27	1.28	Tabes. Feet.
				24.6	.....	.....	31.55	...	...	.....	592	12	.....	9.95	.....	0.95	Right foot in water at 9.5 C.
				24.8	.....	.....	31.57	...	...	.....	247	4	.....	12.52	.....	1.17	Right foot in water at 42.6 C.
				24.9	.....	.....	31.63	...	...	.....	839	10	.....	17.20	.....	1.65	Right foot still in warm water.
		12/ 8/14	96	24.0	37.15	31.90	31.92	426	399	1,065	1,160	8	28.14	30.22	6.60	7.57	Hands.
				24.2	.....	32.06	.....	...	...	629	.....	5	27.46	.....	6.46	.....	Left hand in water at 8 C.
				24.5	.....	32.20	.....	...	...	804	.....	5	36.09	.....	8.47	.....	Left hand still in cold water.
				24.5	.....	32.43	.....	...	...	1,432	.....	9	37.45	.....	8.79	.....	Left hand in water at 43.1 C.
				24.7	37.05	31.98	32.06	1,006	1,001	621	706	10	13.60	15.72	1.35	1.57	Feet.
				24.7	.....	.....	32.05	...	...	.....	880	14	.....	13.96	.....	1.39	Right foot in water at 8.3 C.
Joseph K. ...	48	6/26/12	...	27.3	37.05	31.44	31.43	495	479	2,234	2,121	10	44.24	41.93	8.94	8.75	Hands.
				27.3	.....	31.88	.....	...	...	1,309	.....	10	28.13	.....	5.68	.....	Left hand in water at 8.4 C.
				27.5	.....	32.16	.....	...	...	1,187	.....	7	38.53	.....	7.78	.....	Left hand in water at 43 C.
				27.5	.....	32.42	.....	...	...	977	.....	4	58.61	.....	11.84	.....	Left hand still in warm water.
				26.4	36.95	31.05	30.99	1,280	1,292	537	586	16	6.34	6.85	0.50	0.54	Feet.
				26.7	.....	.....	30.98	...	...	.....	363	10	.....	6.75	.....	0.53	Right foot in water at 43 C.

TABLE OF RESULTS OF CALORIMETRIC MEASUREMENTS IN TWENTY-ONE CASES—(*Continued*)

Case	Age	Date	Pulse Rate	Temperature (C) of Room	Temperature (C) of Arterial Blood	Temperature (C) of Calorimeters Right	Temperature (C) of Calorimeters Left	Volume of Part in c.c. Right	Volume of Part in c.c. Left	Heat Given Off in Gm.-Calories Right	Heat Given Off in Gm.-Calories Left	Heat Given Off in Gm.-Calories In Mins.	Blood Flow in Gm. per Min. Right	Blood Flow in Gm. per Min. Left	Flow per 100 c.c. of Part per Min. Right	Flow per 100 c.c. of Part per Min. Left	Notes
Fred L.	22	11/18/12	88	22.0	37.2	30.56	30.57	385	377	1,626	1,403	13	20.93	18.09	5.43	4.80	Cerebral tumor. Hands.
						30.75	.....	...	...	187	.....	2	16.10	.....	4.18	.....	Left hand in water at 43 C.
						30.97	.....	...	...	1,587	.....	10	31.87	.....	8.28	.....	Left hand still in warm water.
				22.8	.....	31.19	.....	...	...	285	.....	6	8.78	.....	2.28	.....	Left hand in water at 11.2 C.
				22.3	.....	31.25	.....	...	...	599	.....	6	18.64	.....	4.84	.....	Left hand still in cold water.
		11/26/12	100	21.4	37.25	31.35	31.33	389	380	1,652	1,446	13	23.93	20.87	6.15	5.49	Hands.
				20.9	.....	.....	31.48	...	...	.....	320	3	.....	12.51	.....	3.29	Right hand in water at 43 C.
				20.7	.....	.....	31.65	...	...	.....	1,396	8	.....	34.62	.....	9.11	Right hand still in warm water.
				20.7	.....	.....	31.80	...	...	.....	747	11	.....	13.81	.....	3.64	Right hand in water at 10.5 C.
				20.7	.....	.....	31.91	...	...	.....	1,179	11	.....	22.30	.....	5.87	Right hand in water at 43 C.
J. S.	.	4/ 5/12	92	25.9	37.3	30.60	30.64	389	358	749	811	6	20.70	22.55	5.32	6.30	Tetanus. Hands.
				26.2	.....	30.71	.....	...	...	307	.....	4	12.94	.....	3.32	.....	Left hand in water at 43.5 C.
				26.0	.....	30.90	.....	...	...	1,276	.....	6	35.47	.....	9.09	...	Left hand still in warm water.
				26.0	.....	31.08	.....	...	...	355	.....	3	15.18	.....	3.90	.....	Left hand in water at 7 C.
				25.8	.....	31.24	.....	...	...	1,073	.....	5	39.34	.....	10.14	.....	Left hand still in cold water.
Mrs. X.	48	5/11/11	96	27.3	37.35	30.44	30.46	317	326	2,579	2,467	10	44.47	39.23	13.08	12.03	Alcoholic intoxication. Hands.
				27.3	.....	.....	30.82	...	...	.....	268	3	.....	15.22	.....	4.60	Right hand in water at 8.4 C.
				27.3	.....	.....	31.05	...	...	.....	1,309	6	.....	38.48	.....	11.80	Right hand still in cold water.
				27.4	.....	.....	31.27	...	...	.....	403	3	.....	24.57	.....	7.54	Right hand in water at 43 C.
							31.54	...	...	.....	1,493	5½	.....	54.92	.....	15.92	Right hand still in warm water.
John K.	52	5/11/12 (Blood pressure, 180)	108	23.0	37.2	31.38	31.25	475	472	2,676	2,674	12	42.57	41.61	8.96	8.81	Lead poisoning. Hands.
				22.4	.....	31.71	.....	...	...	313	.....	3	21.11	.....	4.44	.....	Left hand in water at 8 C.
				22.3	.....	31.88	.....	...	...	1,330	.....	8	36.29	.....	7.64	.....	Left hand still in cold water.
				22.3	....	32.07	.....	...	...	556	.....	4	50.10	.....	6.34	.....	Left hand in water at 43.2 C.
				22.3	.....	32.30	.....	...	...	1,702	.....	9	42.88	.....	9.02	.....	Left hand still in warm water.
S.	40	4/ 3/12	120	21.8	37.6	30.33	30.46	527	523	2,497	2,624	9	42.40	45.51	8.05	8.71	Lead poisoning. Hands.
						30.68	.....	...	...	410	.....	3	23.55	.....	4.47	.....	Left hand in water at 8 C.
				21.9	.....	30.92	.....	...	...	1,635	.....	6	45.33	.....	8.60	.....	Left hand still in cold water.
				21.5	.....	31.11	.....	...	...	335	.....	3	19.21	.....	3.64	.....	Left hand still in cold water.
				21.7	.....	31.18	.....	...	...	176	.....	2	15.23	.....	2.89	.....	Left hand in water at 43 C.
				22.9	.....	31.35	.....	...	...	1,572	.....	6	40.65	.....	7.71	.....	Left hand still in warm water.
				22.8	. ...	31.60	.....	...	...	879	.....	5	32.55	.....	6.18	.....	Left hand dried and wrapped.
Roderick D.	27	5/10/11	84	26.2	37.1	30.58	30.49	535	513	4,615	4,346	11	68.35	63.54	12.77	12.38	Tobacco. Hands.
				26.3	.....	31.25	.....	...	...	458	.....	2	41.37	.....	7.73	.....	Left hand in water at 8 C.
				26.4	. ...	31.65	.....	...	...	2,748	.....	9	59.00	.....	11.03	.....	Left hand still in cold water.
				26.4	....	32.10	.....	...	...	880	.....	4	46.12	.....	8.62	.....	Left hand in water at 43.5 C.
				26.4	.....	32.42	.....	...	...	1,762	.....	7	56.16	.....	10.49	.....	Left hand still in warm water.
Andrew K.	..	5/17/12	80	23.5	37.25	31.54	31.50	466	463	2,687	2,252	11	47.53	39.66	10.20	8.56	Bullet wound of brain. Hands.
		6/ 6/12	112	23.0	38.15	31.95	32.09	472	460	1,615	2,078	10	28.94	38.10	6.13	8.28	Blood pressure 132.

occipital protuberance. The patient appeared to be in stupor; he did not talk. The right pupil was larger than the left and its outline was irregular. The pupils reacted to light. The external rectus of the right eye was paralyzed. Blood was flowing from the nostrils, but no abrasions were visible in the interior. The tongue protruded in the median line. On the hard palate was a blackish discoloration covering a bullet hole. (It was elicited afterwards that he had shot himself with a revolver.) There was no paralysis; the reflexes were normal. The rectal temperature was 98.8 F. The spinal fluid from the lumbar puncture was bright red, containing much blood. It flowed 120 drops per minute. May 17 the eye grounds were normal. The systolic blood pressure was 140. He voided urine involuntarily. He did not speak, although he was perfectly conscious. There was no Babinski sign. The temperature was 99.8 F. at 8 a. m., and the same at noon. On May 18 he voided urine; the systolic blood pressure was 120. From May 19 to May 21 his condition was the same. On May 24 the systolic pressure was 126, on June 6, 132.

The blood flow in the hands was examined on May 17 and again on June 6. At the first examination he sat quite well in the chair, but was absolutely silent. Hands in bath at 3:05 p. m., in calorimeters at 3:14½, out of calorimeters at 3:28. Pulse 80 (lying down). Room temperature 23.4 C. He kept clutching the stirring feathers occasionally.

TABLE 31.—Calorimetric Measurements in Case of Andrew K.

Time	Right	Left	Room	Time	Right	Left	Room
3:14	31.17	31.17		3:23	31.61	31.52	
3:17	31.22	31.23		3:24	31.64	31.59	
3:18	31.28	31.26		3:25	31.70	31.63	
3:19	31.33	31.33		3:26	31.77	31.70	
3:20	31.39	31.36		3:27	31.81	31.72	
3:21	31.45	31.43		3:28	31.87	31.76	
3:22	31.55	31.52		3:43	31.69	31.59	

Cooling of calorimeters in fifteen minutes, R., 0.18 C., L., 0.17 C. Volume of right hand 466 c.c., of left 463 c.c. Water equivalent of calorimeters with contents, R., 3,468, L., 3,465. Rectal temperature 37.75 C.

Second examination of Andrew K., June 6: So far he has recovered without symptoms. The right pupil reacts to light equally with the left and now there is little difference in size. The right external rectus is still paralyzed. He will now talk freely. Rectal tmperature 38.65 C. Pulse (sitting) 112. Pulse not large. Hands in bath at 1:44 p. m.

TABLE 32.—Calorimetric Measurements in Second Examination of Andrew K.

Time	Right	Left	Room	Time	Right	Left	Room
1:54	31.68	31.67		2:05	31.93	32.07	23.0
1:56	31.66	31.67		2:06	31.965	32.12	
1:57	31.68	31.70	22.8	2:07	31.99	32.155	
1:58	31.70	31.74		2:08	32.02	32.19	23.1
1:59	31.72	31.77	22.8	2:09	32.05	32.23	
2:00	31.74	31.825		2:10	32.08	32.27	23.0
2:01	31.78	31.86		2:11	32.11	32.325	
2:02	31.81	31.92		2:19	32.00		
2:03	31.865	31.97	22.85	2:19½	.....	32.205	
2:04	31.895	32.025					

Cooling of calorimeters, R., 0.11 C. in eight minutes, L., 0.12 C. in 8½ minutes. Volume of right hand in calorimeter 472 c.c., of left 460 c.c. Water equivalent of calorimeters with contents, R., 3,473, L., 3,463.

The patient was discharged cured. He was readmitted July 31 suffering from rheumatism and chronic alcoholism and was discharged "improved" on August 27.

At the first examination of Andrew K., made not much more than twenty-four hours after he was brought into the hospital, the blood flow in the right hand was 10.20 grams per 100 c.c. per minute and in the left 8.56 grams, with room temperature 23.5 C. At the second examination, nearly three weeks later, the flows were 6.13 grams and 8.28 grams respectively for the right and left hands, with room temperature 23 C. He had some fever at the time of the second examination which is perhaps associated with the somewhat smaller flows.[11] It will be noted that on both occasions a distinct difference existed in the rate of flow in the two hands. The fact that there is no constancy in this difference, the greater flow being in the right hand at the first examination, in the left hand at the second, indicates that the differences are of vasomotor origin, but it is impossible to say whether they are related in any way to the brain injury. Our observations on chronic alcoholism, for which in the sequel this man was again admitted to the hospital, would perhaps suggest this rather than the brain lesion as the condition associated with the vasomotor instability. There is, of course, no obvious reason why a bullet wound through a cerebral hemisphere which occasioned no paralysis should cause a permanent difference of flow between the hands, nor indeed any obvious reason why so long as it was not associated with general symptoms it should produce any effect whatever on the circulation in the extremities. As a matter of fact, the average hand flows at the two examinations are quite within the normal range.

SUMMARY

1. In early unilateral brachial neuritis the blood flow in the affected hand was found to be decidedly greater than in the normal hand. This is interpreted as due to partial paralysis of the vasoconstrictor fibers in the nerves involved in the pathologic process.

In long-standing unilateral neuritis with decided atrophy of the affected part, the blood flow is less on the side of the lesion than on the normal side. There is some evidence that one factor in the diminution of the flow may be a change in the walls of the arteries consequent on the injury to the vasomotor nerves, which leads to diminution of the lumen. This may be considered an adaptive change correlated with the diminished function of the part. The diminution in the flow may also be due to the regaining of vascular tone by the paralyzed part, even in the absence of regeneration of its nerve supply.

11. Jour. Exper Med., 1913, xviii, 372.

In peripheral neuritis affecting mainly muscular nerves, the changes in the blood flow of the hands and feet are not so conspicuous, as when the cutaneous nerves are also involved, since a large portion of the total flow in these parts must belong to the skin.

2. In hemiplegia there is, in general, a marked deficiency in the blood flow in the paralyzed members. Considerable differences, however, exist in different cases in this regard, and also in the extent to which the vasomotor reflexes from the normal to the paralyzed part are affected. Whether these differences depend at all on the position of the lesion or are associated with the duration and completeness of the paralysis has not been determined. There is some evidence that reflex vasoconstriction is more easily produced in the paralyzed parts than reflex vasodilatation.

3. In tabes, the blood flow in both hands and feet, but especially in the feet, has been found decidedly subnormal and the vasomotor reflexes feeble.

4. In lead poisoning (without paralysis), the tendency to reflex vasoconstriction was conspicuous. This seemed to be the case also in alcoholic neuritis. In alcoholic intoxication and in a case of excessive cigaret smoking, the opposite was observed, namely, a tendency to marked reflex vasodilatation.

5. It is suggested that, in some cases, examination of the blood flow might aid in the detection of malingering, when the attempt is made to simulate certain neuropathologic conditions. It seems probable that the differential diagnosis, for instance, between such conditions as cerebral hemorrhage and alcoholic intoxication, or between hysterical palsy and paralysis due to an organic lesion, in doubtful cases might be facilitated by blood-flow measurements.

I wish to express my obligations to the staffs of the City Hospital and of Lakeside Hospital for aid without which this investigation could not have been carried out.

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM AND THE MEDULLA OF THE ADRENAL GLANDS, ESPECIALLY MALIGNANT NEUROBLASTOMA

FRANCIS HARBITZ, M.D.
Professor of Pathology, the University of Christiania,
CHRISTIANIA, NORWAY

The morphology and still more the etiology of tumors is as yet an unfinished chapter. Fifty years have elapsed since R. Virchow (1863-1865) published his epochmaking work *Die Krankhaften Geschwülste* and thereby founded the morphology of most of the now well-known species of tumors.

Since then a number of prominent scientists have used the time well. I will mention only Ribbert and his numerous contributions to the subject of tumors. But still new forms are discovered or formerly not well understood forms are reclassified. Such is the case with regard to the group of neoplasms this paper is to discuss—certain tumors of the nervous system and of the adrenal glands. These peculiar growths have formerly been classified as sarcoma, the storeroom containing so many incongruous matters which need a thorough putting to right. This process is, however, progressing, as pathologic new formations which prove to be of an inflammatory nature, for example, the lymphogranuloma or independent species of tumors which according to their structure and genesis should have been excluded from the ordinary forms of sarcoma, are being separated.

It is a well-known fact that tumors may originate from and consist of elements of nervous tissue. Best known are the not infrequent and important glioma of the central nervous system and of the retina. The so-called neurofibroma occurs frequently. Of especially great interest from a general pathologic and clinical point of view are the multiple growths of this kind, the multiple neurofibroma with its many different forms. I have in an earlier paper gone more thoroughly into this matter.[1] The origin of neurofibroma is generally conceded to be the connective tissue of the nerve trunks, but this is as yet not universally accepted, as certain authors (Verocay, Herxheimer) doubt this theory and maintain that the cells of the sheath of Schwann form the matrix. As these cells are supposed to belong to and originate from the nervous system the new growths arising from them would

1. Harbitz, Francis: Multiple Neurofibromatosis (von Recklinghausen's Disease), THE ARCHIVES INT. MED., 1909, iii, 32.

be of ectodermal origin and would be classified with glioma. These different opinions are not yet settled.

Another tumor is described and a separate place claimed for it, namely the ganglioneuroma, a tumor containing ganglion cells and nerve fibers, a genuine neuroma in distinction from the just mentioned "pseudoneuroma." The existence of such tumors has been maintained from Virchow's time, but the reports have not gained absolute confidence; these tumors are considered very rare. Personally, I have never seen an assuredly certain case of ganglioneuroma if as such are not classified the nodes found in nodular sclerosis of the brain. In recent years new observations have shed light on this subject, and as a result of newer and better methods of differentiation of the component tissues of the nervous system it now may be safely assumed that ganglioneuroma does occur but seldom and then often in varying morphologic forms.

J. H. Wright has shown conclusively that certain peculiarly constructed tumors arise from the sympathetic nervous system and from the medullary portion of the adrenal glands. These tumors consist of immature and undifferentiated nerve tissue of a characteristic structure and are eminently malignant in their development and course.

It will be well to review the embryologic origin of the sympathetic system[2] in order to understand the development and structure of these neoplasms.

The adrenals are developed from a divided source. Their cortical portion comes into existence as early as the fourth week of fetal life, supposedly from a thickening of the celomic mesothelium, and becomes merged into a joint organ, the mesonephros, which may be easily recognized in the eighth week. If this persists it results in the permanent union of the cortices of both adrenals as well as in the occurrence of accessory (supernumerary) adrenals in other locations, which all consist of cortex although often somewhat abnormal in structure. From such cortical remnants are developed the socalled "hypernephromas," one of the most frequent neoplasms of the kidneys, a genuine ectodermal and epithelial growth.

The medulla is derived from the sympathetic system whose elements travel into the cortical portion and subsequently aggregate in its center. To this fact is due the close relation between the adrenals and the sympathetic system. The primary formative cells of the medulla, the mother cells of the sympathetic ("sympathogonier"), are small cells with few fibers and intensely colored nuclei. They are numerous, lymphocyte-like, with sparse protoplasm, and give no reaction with the chrome salts.

2. Based on the work of Kohn.

Later, during the third and fourth month, the cells differentiate into (*a*) sympathetic ganglion cells with fibers, (*b*) into larger cells containing large clear nuclei, polymorphous, cylindrical and epithelium-like, often arranged in bands. Their protoplasm and to some extent their nuclei give fine brown to greenish granulations with chrome solution so that microscopically the tissue appears brown. These cells are consequently named chromaffin, chromaphil or facochrome cells.

Such chromaffin, epithelium-like cells are also found scattered among the ganglion cells and fibers and are found in heaps in certain locations as in the carotid ganglion (about the size of a pea, at the bifurcation of the commoin carotid) which also contains ganglion cells and nerve fibers. They are found in the organ of Zuckerkandl, especially prominent in fetal life and newborn children, a flat body from 3 to 20 mm. long, situated on the anterior aspect of the aorta, around the inferior mesenteric artery. This organ contains as a rule no ganglion cells. Finally they are found in the coccygeal ganglion, a simple, nearly pea-sized organ on the anterior lip of the coccyx. These larger accumulations of chromaffin cells are also named paraganglia, and all chromaffin tissue collectively, the chromaffin system.

This system arises then from the sympathetic nerve and this large, widely branching nerve has its origin, partly from motor nerves of the spinal cord, partly from the spinal ganglia, and it contains primarily fibers and cells—"neuroblasts"—in groups, the first formation of the sympathetic ganglia. The paraganglia, hence, are only a part of those migrated cells and fibers endowed with special differentiation and have their ultimate origin in the ectodermal tissue. Kohn maintains that heaps of undifferentiated embryonic nerve cells, "neurocytes," may be retained here and there in the nerves in a latent condition, later to take on renewed activity and develop into tumors of various kinds.

Tumors arising from the adrenal medulla or from the sympathetic system, collectively termed neuroblastomas, as we now know may be very differently constructed. This is due to various stages of development in which the cells giving rise to the tumor were at that particular time. Schematically we may have: 1. Tumors consisting of fully differentiated nerve tissue with ganglion cells and nerve fibers, usually termed ganglioneuroma or genuine neuroma. 2. Tumors made up of chromaffin cells in the sympathetic or parasympathetic tissues termed paraganglioma, mostly of an epithelial nature. 3. Tumors composed of undifferentiated sympathetic formative cells, the so-called malignant neuroblastoma, relatively frequent and important growths, whose real nature first has been understood in recent years.

Transitional as well as mixed forms are encountered as might be expected from the manner in which the sympathetic system and the

adrenal medulla are developed. It also appears as if the mixed forms occur more frequently than formerly supposed (Landau, Martins, Wahl). All three forms may be found combined in the same tumor or in the same individual (Landau's case[3] and particularly a case described by Wahl[4] of three primary lesions in a 1½ year old child). Besides it is a fact that heaps of undifferentiated cells are found deposited in the characteristic growths (ganglioneuroma or chromaffin tumor). In a few of these tumors mesodermal as well as ectodermal tissue have been placed side by side (as myeloid, adipose and muscular tissue).

Transitional forms are also found. The malignancy seems to decrease in proportion to the advanced stage of differentiation and the increasing age of the host, while on the other hand, the differentiation of the embryonic tissue into ganglioneuroma and chromaffin tumors increases in ratio to the age of the individual.

We shall first discuss the malignant neuroblastomas of which this paper mainly treats. Attention had for a long time been called to the fact that malignant tumors now and then occurred in the adrenals and the liver of newly born infants and quite young children. These neoplasms, in which were found large necrotic areas and hemorrhages, were mostly regarded as lymphosarcoma and round-cell sarcoma and described as such, especially by English and American authors in the eighties and nineties. In the Norwegian literature two cases are described by F. G. Gade, one of which, according to the description in all main features, corresponded with neuroblastoma.

Little by little it became evident that these growths had certain structural peculiarities in common with the nervous system. Such stress was laid on the similarity of the tumor structure with glia tissue that they were named glioma (Ribbert and his pupil Küster). However, comparatively early, a deeper understanding of these growths was shown in the works of Marchand (1891), who maintained that the tumors were made up of embryonic undifferentiated cells of the sympathetic system (which was also pointed out by Kretz and particularly by Wiesel).

But the generally accepted view, which later was recognized as correct, that these tumors arise from embryonic, sympathetic nerve cells, neurocytes, directly, was first conclusively proved by James H. Wright[5] in 1910. He introduced the name neurocytoma or neuroblastoma. Later followed a number of papers on similar tumors, among which may be mentioned the more exhaustive ones by Pick and

3. Landau: Frankl's Ztschr. f. Path., 1912, xi.
4. Wahl: Jour. Med. Research, 1914, xxx.
5. Wright, James H.: Jour. Exper. Med., 1910, xii.

Bielschowsky (1912)[6]; Landau (1912) and Herxheimer[7] (1913), Wahl (1914).

The peculiar structure of these tumors as first minutely described by J. H. Wright is as follows: The growths are made up of numerous, closely packed, small, atypical cells with strongly colored round or oblong nuclei, a scanty protoplasm, and with partly faint processes, often forming a kind of syncytium, appearing like the embryonic, undifferentiated cells of the sympathetic system. Between the cells is a more or less distinct, finely fibrillated network, which has been definitely proved to be nerve fibers. No ganglion cells are present. The cells are often arranged in characteristic rosette form, with a pale colorless center composed of numerous fibrillae, surrounded by radiating, cylindrical cells, as in the structure of certain gliomas of the retina and the central nervous system.

Then again the cells are arranged in larger heaps and the fibrillae are separated by strands of connective tissue or in bundles which taper into colorless fibrillar strands. At times no differentiation is found. These fibrillae are not glia fibers nor connective-tissue fibers, but in all probability are embryonic nerve fibers. The structure greatly resembles a round-cell sarcoma, a glioma, a lymphosarcoma or an alveolar sarcoma. The tumors are congenital. They are only found in the newborn, in infants or in children, who have died during the first years of their existence. About thirty cases have been described up to the present, all in children, of which twelve were not above 3 months of age, eighteen not above 1 year, and only eight in twenty-six being more than 1 year old. The oldest child in whom such a tumor was demonstrated was 9 years old. The growths occurred twice as often in girls as in boys. Whether this is just a coincidence, cannot be determined now. The site of the tumors was most frequently in the adrenals, in a few cases in the sympathetic nerve and once in the coccygeal gland. As a rule they are single, at times multiple; the disease is hardly systemic. They are exquisitely malignant. Their growth is infiltrating and progressively destructive; they have a tendency to cause necrosis and hemorrhages and to form metastases, through the lymphatics to the lymph glands as well as through the blood vessels preferably to the liver, in which may be found scattered nodes or a diffuse infiltration; and sometimes but seldom to the osseous system, and then, especially to the cranium or to other internal organs. The structure of the metastases is often so atypical that only a diagnosis of sarcoma can be made.

---

6. Pick and Bielschowsky: Ztschr. f. d. Gesellsch. f. Neurol. u. Psychiat., 1911, vi.

7. Landau and Herxheimer: Beitr. z. path. Anat. u. z. allg. Path., 1913, lvii.

In order to throw some light on these growths I shall briefly relate some of my own observations during recent years.

Case 1.—June 7, 1913, I received from Dr. Justus Barth a tumor which he had just removed from a 3-year-old child. It was situated anteriorly on the sacrum and was very difficult to remove as it had infiltrated the surrounding tissues and also the large pelvic veins. One of these became perforated so that it had to be sutured. As a consequence of pulling on the tumor, the child's pulse became very feeble — the tumor seemed to be closely connected with the sympathetic nerve. The child, who had lost considerable blood, died on the table. No signs of metastasis were present; a post-mortem examination, however, was not made. The tumor was orange-sized, somewhat oblong, of a very soft consistency. It was surrounded by a connective-tissue capsule, which was penetrated in several places, especially in a larger (5 by 7 cm.) area, where the substance was greatly broken down, quite mushy and soft; color, yellow or yellowish-red. On section the surface showed partly a more grayish,

Fig. 1.—Section of neuroblastoma. Numerous rosettes and tubes surrounded by neuro-epithelium.

partly a more yellowish color, particularly in those places where extensive necrotic changes had taken place. Those areas were intensely yellow in color. Hemorrhagic foci were not seen. It was found that the tumor was subdivided into smaller and larger nodules or spaces in which were deposited quite soft, grayish-white tumor masses. On the surface, corresponding to the nodules, were many small protuberances.

Microscopic Examination.—On first sight the structure reminded one of an epithelial tumor, but on closer examination it proved to be an embryonic not yet differentiated nerve tissue. The major part of the growth was necrotic to such an extent that its structure only could be recognized in small sections. It was made up of numerous small cells with highly colored nuclei and very sparse protoplasm. The cells were closely packed and separated by a faint fibrillar network. The cells were atypical; from them alone no conclusion could be drawn as to their nature, but their mode of arrangement brought

out their peculiarities. They were arranged in larger, well-defined groups surrounded by heavy connective-tissue walls.

The structure presented a varying view. Most often the cells were arranged in long, tortuous bands, the cells close together, side by side in one or more layers (Fig. 1). When several bands ran parallel to one another, long, adenoma-like formations were produced. Their periphery was formed by cylindrical epithelium-like cells. The centers were filled with fine, fibrous or granular masses, organically connected with the peripheral cells. The whole "tube" was separated from similar tubes by a sparse, vessel-carrying, connective tissue framework.

Where the "tube" was cut across, rosette-like formations were seen, that is, a layer of strongly colored small cells around a fine-fibered granular mass in the center. Rosettes formed by closely packed cylindrical cells around a small vessel were observed also (Fig. 2). The tumor was principally made up of these cellular structures, but in close organic connection were seen other areas,

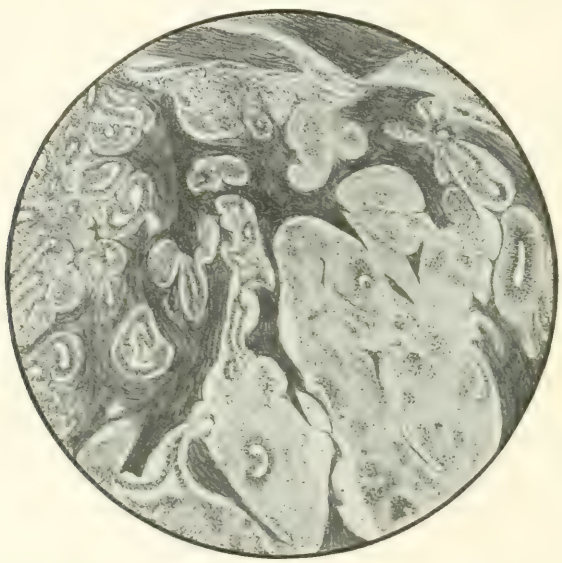


Fig. 2.—Neuroblastoma. Undifferentiated nervous tissue in large masses with rosettes. Above numerous rosettes and tubes.

poorer in cells, paler and more decidedly fibrillar. Here the cells were more fusiform, had small, oblong nuclei and almost no demonstrable protoplasm, but were surrounded by a fibrous substance, which often arranged itself into long bundles. Large heaps of cellulofibrillary areas again formed sharply defined accumulations of tumor tissue well separated from the surrounding connective-tissue stroma (Fig. 3). Finally were seen large heaps of the very small cells with round nuclei and very sparse protoplasm in an almost confluent arrangement, forming a kind of syncytium or multinuclear conglomeration, that is, the cells were packed more closely together, but without being differentiated into rosettes. These parts of the tumor gave the impression of representing a still more undeveloped stage of the growth.

Case 2.—Another case of neuroblastoma, a primary cystic tumor of the adrenal with liver metastasis, occurred in a 6½ year old child. As the case gave the same microscopic picture as the former, it will be presented only in

its main features. The child was sick for about one month with signs of a rapidly growing tumor of the liver. Post-mortem examination revealed a considerable enlargement of this organ which was studded with soft, grayish-red, large, partly hemorrhagic nodules. The left adrenal was converted into a fluctuating "cystic" mass, as large as a goose egg, containing a bloody fluid mixed with tumor particles. Microscopic examination showed in the wall of the cyst a tissue consisting of atypical, quite undifferentiated cells which, as to shape and arrangement, entirely corresponded with those found in the first case.

In the older Norwegian medical literature are two cases of primary adrenal tumors described by F. G. Gade. These had their starting point in the adrenals of children 4 and 6 years old. They were described as and were supposed to be round-cell sarcomas. It must be assumed, however, in the light of our present knowledge, that they were malignant neuroblastomas.

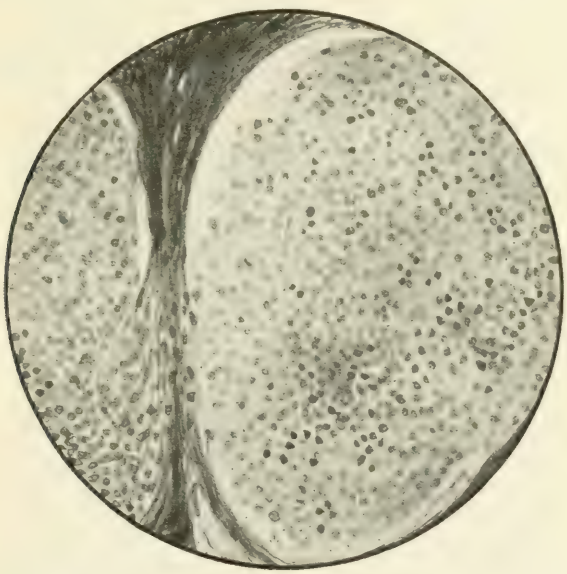


Fig. 3.—Numerous clumps of cellular nervous tissues.

In connection with the two cases of genuine, malignant neuroblastomas must be briefly mentioned a case of teratoma in which proliferation of nerve tissue was the most characteristic feature and which developed into tumors that structurally gave all evidence of being neuroblastomas. It is not uncommon that teratomas in the most different locations as, for instance, in dermoid cysts of the ovary, contain comparatively large masses of nerve substance in a lively process of development. Such great masses as in Case 3, however, are seldom encountered and add to its particular interest, as almost the entire tumor was a neuroblastoma. Judging from the great masses of

nerve tissue which make up this and similar tumors, it seems rational to suggest that possibly some malignant neuroblastomas originally have been teratomas in which the nerve elements mainly proliferated and finally took the lead. The existence, repeatedly proved, of other tissues in such tumors might also speak for this assumption.

Fig. 4.—Tumor in sacral region.

Case 3.—In the fall of 1905, Dr. J. Barth, assistant physician to the Maternity Hospital at Christiania, sent me a malformed fetus with a large tumor of the sacral region. The fetus was 17 cm. long, almost normally developed and about 4 months old. From the gluteal region reaching from the penis and scrotum toward the loins proceeded a pyriform growth measuring in length 7¼ cm., in width 6½ cm., and in thickness 3½ cm. Its greatest circumference was 15 cm. (Fig. 4). The somewhat narrower part connecting it with the body of the fetus measured 9 cm. Fetus and tumor weighed 250

grams. Except at its inferior pole the neoplasm was covered with integument. The surface was even and smooth. The consistency somewhat uneven, mostly soft. The integument was not everywhere firmly attached. On its entire anterior aspect it formed only a membrane loosely connected with the inside. Posteriorly it could be separated from the underlying tissue only at its inferior extremity. After cutting through and lifting up this membrane anteriorly the following picture was revealed:

Three oblong rounded bodies were separated by relatively deep furrows which, however, posteriorly were united by a common substratum. Between the two first eminences ran a band 2 cm. wide which gradually merged into the substance of the third. On section these three tumors had a nearly similar appearance. They were covered with a thin, smooth membrane, and consisted of a soft grayish to yellowish almost necrotic tissue which broke into fragments on being cut. On opening the central canal of the sacrum it was found closed posteriorly. A communication reaching about into the center of the tumor seemed to be maintained below. This, however, could not be definitely decided on account of the softened condition of the tissues.

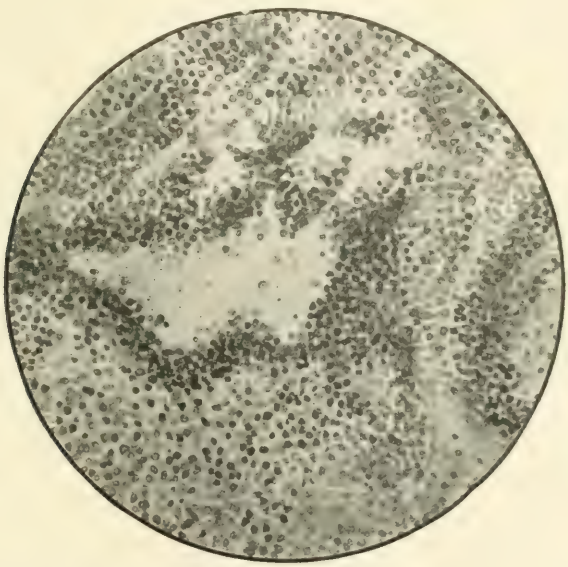


Fig. 5.—Large masses of atypical, undifferentiated nervous tissue with indication of a large rosette.

Microscopic Examination.—The various sections of the tumor contained the same kind of tissue: large accumulations of small round cells with large nuclei and sparse protoplasm subdivided by connective-tissue strings. The exceedingly numerous cells were mostly in large heaps with no characteristic arrangement. They were closely packed almost without intercellular substance (Fig. 5). Only here and there where they were less numerous was seen an indistinct granular or fibrillar intercellular substance which was colored yellow with Van Gieson's stain. In other places the cells were arranged in a more characteristic manner, forming large wavy bands, the cells being placed in rows of 6, 8 or 10, otherwise in the same atypical way as elsewhere. The tissue around the cells was devoid of nuclei and consisted only of a finely granular, or in places of an indistinct fibrillar, intercellular substance. Finally places were observed where the cells had arranged themselves in rosettes around an

oval or circular space filled with heterogeneous granular or fibrillar tissue (Fig. 6). In other words the tumor mass consisted of embryonic, proliferating, not yet differentiated nerve substance. The arrangement reminded one somewhat of an ependyma around the central canal. The tumors also contained a few lumps, which supposedly were embryonic cartilage.

The microscopic structure corresponded in every detail with the structure of neuroblastoma, and the tumor should be classified as such. The presence of some embryonic cartilage has no contrary bearing.

The most recently described group of tumors coming under this head is the paraganglioma or chromaffin tumor. This has as yet only been demonstrated in a comparatively small number, about 12 or 15 up to the present, mostly since 1909. The frequency has increased greatly during the last year since they have received more attention.

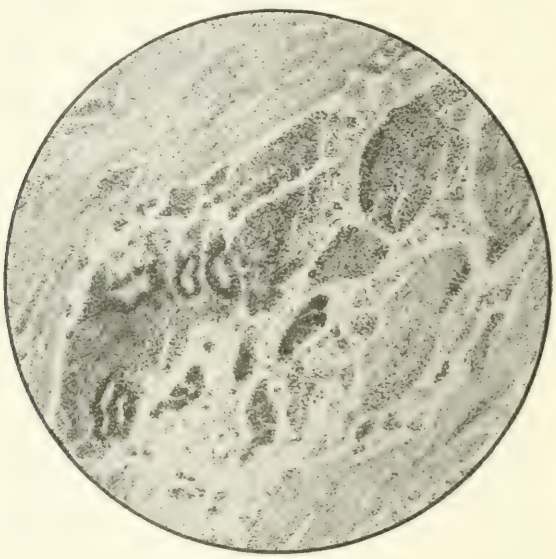


Fig. 6.—Nervous tissue, slightly differentiated, with several rosettes.

The paraganglioma may develop from any of the paraganglia of the sympathetic nerve, but most frequently from the medulla of the adrenals ("struma suprarenalis medullaris") and the carotid gland. A single case has been observed in the region of the coccygeal gland, supposedly originating from it. These growths are sharply limited, mostly solitary, occurring as a rule in more advanced age, with about equal frequence in men and women. They are often casually detected at postmortem examinations. They should be considered as typically benign tumors with a characteristic structure, made up of large epithelial-like cells arranged in heaps, separated by a very sparse, vessel-carrying stroma "peritheliomas" (as in organs with an internal secretion). The cells are chromaffin and contain adrenalin, a fact

which may be readily demonstrated by the fixation fluid in which it dissolves. This is, however, not always the case, because the cells may be in a transitional, not fully developed stage, and hence may not yet have acquired the chromaffin property. These tumors should be considered as epithelial growths on the borderline between typical and atypical neoplasms. Of great interest is the fact that some of them appear more as diffuse hyperplasias, especially in the adrenals, and that they repeatedly have been found in individuals afflicted with multiple neurofibromatosis as, for instance, in the sympathetic nerve.

The most important reports on tumors of the adrenal medulla are the following:

Manasse (1896): A tumor the size of a hen's egg in the medulla of the adrenal in a man aged 70.

Stange (1902): A round tumor, size of an apple, of chromaffin tissue in the sympathetic nerve of Zuckerkandl's organ. The tumor consisted of polymorphous cells and giant cells, which were colored yellowish-brown with chrome salts.

Suzuki:[8] Three cases in the adrenals; (1) a 10 cm. large, round tumor in the adrenal of a man aged 62, (2) a tumor 0.5 cm. large in a woman aged 60 with multiple neurofibromatosis, and (3) a similar tumor in a woman aged 82.

Wiesel and Neusser: A tumor in the adrenal of a man aged 43. The tumor was cystic and hemorrhagic and made up of chromaffin and other cells of the sympathetic nerve.

Hedinger[9] in 1911 described a "struma medulla cystica suprarenalis," an 11 cm. round tumor in a 37-year-old woman. The tumor contained large polymorphous epithelium-like cells with alveolar arrangement separated by narrow connective-tissue septa, abundantly supplied with blood vessels, also large giant-cell-like formations without adipose tissue but partly with glycogen. Some gave the typical brown color with chrome. It contained also possibly some ganglion cells, besides bundles of nerve fibers. The structure reminded one considerably of hypernephroma.

Herde[10]: Two cases, (1) a 6 or 7 cm. sized tumor, hemorrhagic and cystic, with chromaffin cells, in a 62-year-old woman; (2) bilateral suprarenal tumors in a 45-year-old woman (1 and 3 cm. in diameter, respectively). These growths were made up of chromaffin cells and giant cells.

Wegelin[11]: A 5 cm. sized tumor with chromaffin cells and adrenalin in the solution (brown color) in a 39-year-old woman. The cells were quite polymorphous.

---

8. Suzuki: Berl. klin. Wchnschr., 1909, 1910.
9. Hedinger: Frankl. Ztschr. f. Path., 1911, vii.
10. Herde. Arch. f. klin. Chir., xcvii.
11. Wegelin: Verhandl. d. Path. Gesellsch., 1912.

Kowashima[12] found in a case of multiple neurofibromatosis a diffuse hyperplasia of the adrenal medulla. He thinks that both diseases are the same, namely a congenital anomaly which may affect the cerebrospinal, the sympathetic and the peripheral nerves and the adrenal medulla with its chromaffin cells.

Herxheimer[13] found in a 55-year-old man afflicted with neurofibromatosis, a tumor in the suprarenal capsule as large as a hazelnut. Some similar growths in the carotid gland should be mentioned, namely, a case described by Marchand, 1891, by Oberndorffer,[14] and by Mönckeberg.[15] The last was a tumor in the carotid gland of a 52-year-old man. Beitzke describes "struma intercarotica." It was a plum-sized brownish-red tumor of characteristic structure in an old woman of 56. The tumor varied in appearance in periphery and center. In places were large nuclei, rich in chromatin.

The benign tumors of the carotid gland are as a rule found in grown people from 16 to 74 years of age. Most of them have been surgically removed. They were intimately connected with the carotids, brownish-red to grayish-brown in color, of varying consistency, well supplied with vessels, alveolar in structure and more or less similar in character to the structure of the carotid gland.

To these cases of tumors in the adrenal medulla may be added a case of multiple tumors, some of which may be supposed to have started in the adrenal medulla.

Case 4.—Multiple tumors: (1) Hypernephroma in a kidney; (2) cystadenoma in the pancreas; (3) chromaffin tumor in the region of the suprarenal capsule and (4) a similar tumor in the region of the kidney. This patient, a man aged 47, died from a large abdominal neoplasm of the left renal region. It had given symptoms for about one year. At the post-mortem examination the following conditions were found:

(1) The left kidney had been converted into a large tumor reaching from the superior spine of the ileum to the diaphragm. It was retroperitoneally situated. Its surface was studded with large nodules and it was very soft. Remnants of renal tissue were seen in places as a thin covering of the tumor. It consisted to a great extent of large, yellowish-white, necrotic material which in places was broken down forming a soft, reddish-gray, almost pus-like mass. In the periphery were less necrotic, reddish-gray tumor nodules. The renal veins were filled with the same grayish-white tumor masses extending into the inferior vena cava which was filled entirely with a cylindrical, yellowish-red tumor mass reaching clear into the right atrium of the heart. In the right kidney at its superior pole were soft reddish-gray tumor nodules — metastases from the tumor of the left kidney. Numerous metastatic deposits of the same nature were also found in the lungs and liver.

Microscopic Examination.—In the principal tumor of the left kidney and in the metastatic growths it concerned the same structure, namely hyper-

12. Kowashima: Virchow's Archiv. f. path. Anat., 1911, cciii.
13. Herxheimer: Beitr. z. path. Anat. u. z. allg. Path., 1913, lvii.
14. Oberndorffer: Centralbl. f. allg. Path. u. Path. Anat., 1905, xvi.
15. Mönckeberg: Beitr. z. path. Anat. u. g. Allg. Path., 1905, xxxviii.

nephroma. The stroma was a sparse, connective-tissue reticulum with vessels; the long, solid alveoli were filled with large clear epithelial cells with oval, distinct nuclei and a clear colorless protoplasm. The same regular structure was found throughout, corresponding with the usual picture of a hypernephroma and had structurally no similarity to the "brown tumor."

(2) In the tail of the pancreas was a conglomeration of cysts. One of these was as large as a walnut and was filled with a clear yellow fluid. In its walls were trabeculæ with prominent edges and in the walls of the large cysts could be seen the outlines of smaller ones.

Microscopic Examination.—This revealed scattered larger and smaller cysts, which were lined with a single layer of flattened epithelium, in places detached into long ribbons. The walls around and between the cysts consisted of a hyalin connective tissue with small deposits of pigment and poor in cells. The parts of the pancreas in close proximity to the tumor, showed normal conditions. No transitional stage between the tumor and the pancreas can be demonstrated. Diagnosis: Cystadenoma of the pancreas.

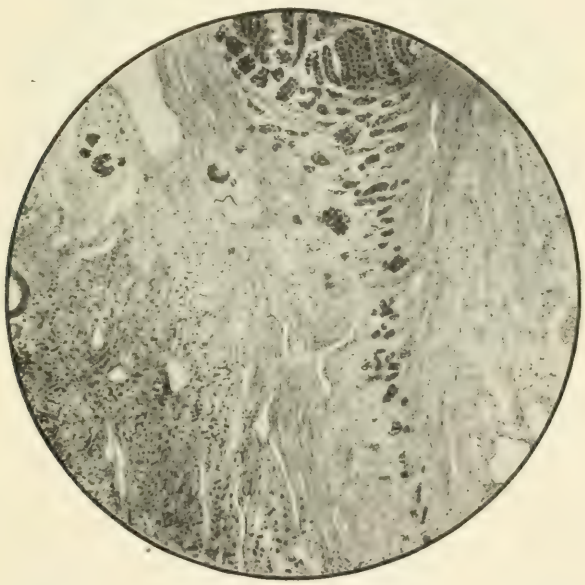


Fig. 7.—Irregular distribution of adrenal substance in boundary between tumor and adrenal.

(3) To the inner side of the upper pole of the right kidney and loosely connected with it by connective tissue was a round tumor 6 or 7 cm. in diameter sharply limited and covered with a hard calcareous capsule. Inside of this was a soft mass grayish-red or grayish-brown in the periphery and gray-white in the center; somewhat spongy and cystic.

The tumor showed on section a great many thick-walled vessels containing blood and lined with a regular layer of endothelium. The walls of the vessels were in many places greatly swollen and hyaline. In the softer parts was a hyaline connective tissue, poor in cells, with long narrow bands of proliferating, angular, polymorphous cells with large nuclei, resembling endothelial or epithelial cells. Everywhere was an abundance of vessels with marked hyaline degeneration. In the periphery of the tumor were epithelium-like cells arranged in small heaps, irregular in shape with large nuclei, rich in chromatin. Diagnosis: hemangioma. Brown tumor from adrenal tissue (?).

(4) Above the right kidney, loosely connected with the tumor just described, and to the right kidney was a sharply defined, soft, grayish or brown tumor, resembling somewhat liver tissue. It consisted of two parts, the larger the size of a large walnut, the smaller larger than a hazelnut, united by a fibrous capsule. On section was seen a homogeneous, spongy surface with some larger and smaller spaces. On the upper surface were parts of the right adrenal, especially of its cortical portion. The growth was situated between the right kidney and the adrenal. It was, however, entirely separated from the kidney by fibrous tissue, but was intimately connected with the adrenal, which gradually merged into the tumor, especially at the hilus; at a point where the two nodules joined, adrenal tissue abundantly supplied with vessels penetrated into the neoplasms.

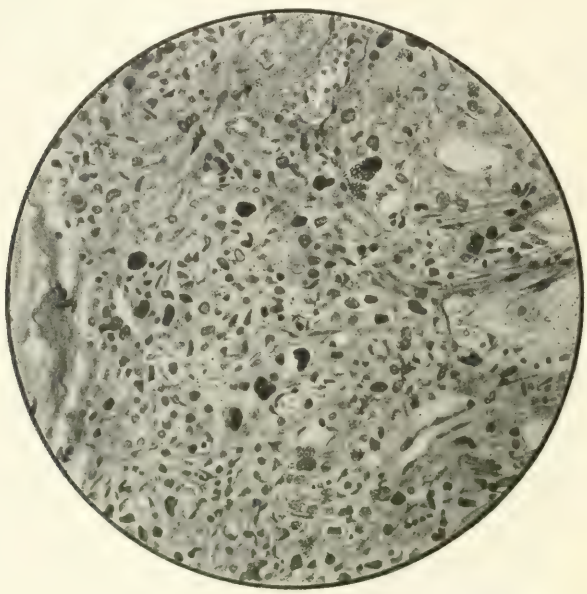


Fig. 8.—Large, irregular, more or less polyhedral cells forming parenchyma of tumor.

Microscopic Examination.—At the point of junction with the adrenal was an irregular distribution of suprarenal tissue in a heavy fibrous band forming the boundary between the tumor and the adrenal. Distributed in the fibrous tissue were islands of epithelium of the same kind as in the cortical portion of the adrenals. Such islands were also scattered along the fibrous borderline, in a few places on the surface of the tumor, but particularly in a narrow strip of fibrous tissue which continued into the tumor (Fig. 7).

The medullary portion was somewhat irregularly arranged in certain parts. Scattered heaps of somewhat atypical epithelium occurred in a spongy (lymphangiomatous?) tissue with several nerves. The tumor was very rich in cells of many shapes, but otherwise homogeneous in its structure. The abundant supply of vessels and nerves was striking. It contained a multitude of blood vessels, many with very thin walls. Others had swollen walls with hyaline degeneration and few cells. In other places was a fine fibrillar network with narrow slits — edematous. There were also numerous large and small blood and lymph vessels and larger spaces (sinuses) lined with endothelium, giving the structure a great resemblance to a hemangioma or lymphangioma. It was also traversed by numerous large branching nerves whose twigs were

ultimately lost between the tumor cells. In many places was an amorphous, yellowish pigment, apparently remnants from hemorrhages.

The tumor parenchyma was made up of large, irregularly shaped, angular, polyhedral, sometimes round, more or less epithelial-like cells. The nuclei were also irregular in shape, partly large and swollen and partly multinuclear. They were arranged side by side in small heaps or bands without discernible intercellular substance, but with a fine connective-tissue network separating the heaps. The similarity to the medulla of the adrenals was quite noticeable in places. Many cells had a faint brownish pigmentation. Some had a good deal of granular protoplasm; others had very large nuclei with abundant chromatin; a few had multiple nuclei. Beside these epithelial cells were numerous smaller connective-tissue-like cells arranged partly as a connective-tissue stroma among the tumor tissue. Finally were observed, scattered small atypical round lymphocyte-like cells, although nowhere could a genuine inflammatory infiltration be demonstrated. Ganglion cells or cells similar to these were not found. In specimens fixed with chrome solution were some few large polyhedral cells with diffusely brown colored protoplasm. It is to be regretted that the post mortem was not made before about twenty-four hours after death. The alcohol in which the tumor later was preserved did not turn brown or give the reaction for adrenalin.

This case is very interesting in many respects. First on account of the multiple neoplasms of—at least apparently—entirely different kinds of growths in various organs, in the pancreas, the adrenals, and free in the abdominal cavity. The polymorphous nature of the tumors, however, may not have been so great because the tumors were principally epithelial—a cystadenoma in the pancreas, a large atypical hypernephroma in one kidney with metastatic deposits, arising from the epithelium of the adrenal corticalis—further an adenomatous or "strumous" growth arising from the medullary portion of the other adrenal. But to these was added the evidently very old abdominal tumor well surrounded by a calcareous capsule. This tumor on microscopic examination gave the impression of being a hemangioma arrested in its growth. On renewed and closer investigation, however, it was found that more importance should be attached to the remnants of the original tumor or parenchyma disclosed in the grayish-brown strip along the periphery of the growth, which was made up of small heaps of polymorphous, epithelial-like cells, practically identical with the cells of the struma of the right adrenal. When the intimate connection with the "brown tumor" of the adrenal is considered, the evidence goes in favor of assuming, that both had the same origin, with the reservation, however, that the encapsulated tumor, which now consisted mainly of blood vessels or more correctly speaking remnants of such, was a further step in the development of the brown tumor, that is, it had been arrested in its growth. The tumor parenchyma was mostly degenerated and the blood vessels hyaline. This is most likely the correct interpretation, and if so, this tumor must also be classified with the epithelial growths. Very interesting were the scattered

islands of adrenal tissue found in the capsule, which surrounded the brown tumor and also in the adjacent parts of the right adrenal. These represented principally the cortical portion. It was further of the greatest interest that these *verirrte keime* were found in the right adrenal coincidently with an atypical hypernephroma of the other side. To assume that a similar abnormality might be the starting point on the left side seems reasonable. Great stress should be laid on the intimate connection between the "brown tumor" and the right adrenal as well as on the existence of isolated islands of adrenal medulla and supposed growth of development of the brown tumors from the medulla of the adrenals.

The microscopic conditions, the gradual transitions and the brown color point decidedly in favor of this theory. Still more conclusively does the microscopic picture strengthen the evidence—the description which so far as conclusions can be drawn from a fixed specimen shows that the tumor cells and the entire tissue correspond in structure and appearance with that of the adrenal medulla in the most normally constructed parts, while they deviate more and more therefrom in the more cellular, atypical sections.

Important points in the diagnosis of chromaffin tumor are the great abundance of vessels in places and the rich vascular supply of the stroma (see the hemangioma-like structure of the tumor next to the abher from which the capsule has been removed); next the existence of nerves, although nonmedullated, in the tumor—a frequent occurrence—which, however, also speaks in favor of adrenal origin; further, the similarity to other tumors of the same type (Hedinger's case), and finally the brown color of the tumor itself and the fact that some, although only a few, of the large epithelial-like cells took on a brown color after having been treated with the chrome solution. The postmortem examination was unfortunately made so late that the chances of obtaining chrome fixation were slight, so that the characteristic color was obtained only in a few places. Another diagnostic point would have been the chemical demonstration of adrenalin in the extract from the tumor (as in aqueous extracts obtained from normal, adrenalin tissue), but the attempts in this direction had a negative result.[16] Everything taken into consideration, it seems certain that

16. An extract is made from quite fresh adrenal tissue in physiologic salt solution. After standing for about eighteen hours, adrenalin can be demonstrated in the extract by the following procedures: (1) By treatment with a dilute solution of ferric chlorid — Fe_2 Cl_6 — a greenish-yellow color turning into reddish is obtained (Vulpian's reaction); (2) with dilute tincture of iodin a reddish color is obtained; (3) with a dilute 0.1 per cent. potassium sulphate solution a red color is obtained; (4) with a 2 per cent. muric chlorid solution and heating, a red color develops (Camesatti's reaction).

this adrenalin tumor (and also very likely the other hemangioma-like) originated in the medullary substance of the adrenals, being to a great extent chromaffin. In other words the tumor should be classified as a paraganglioma, possessing as it does the typical qualities of these neoplasms—a classification which also is corroborated by a former accidental find at the postmortem of an elderly man. One of the tumors was even arrested in its growth, had been encapsulated and had to a great extent undergone degenerative changes.

POTASSIUM POISONING IN NEPHRITIS *

WILSON G. SMILLIE, M.D.
BOSTON

Functional studies of the kidney have afforded many striking possibilities and many interesting problems. The subject is so new, the methods so exact, and the interpretation of results so little understood, that the subject is an ideal one for research.

During the past year, I[1] had an opportunity to study with Dr. Frothingham the different nitrogenous diets in chronic nephritis from a functional point of view. In these cases, we found, as has been demonstrated by Widal[2] and others, that certain types of chronic nephritis were unable to excrete salt normally. In many cases, 10 gm. of sodium chlorid, when added to the diet, was excreted poorly, or not at all.

Bunge,[3] several years ago, in observations on animals and normal individuals, found that the increased intake of potassium salts caused an increased sodium salt excretion, and vice versa. This observation suggested to us the possibility of causing an increased sodium salt excretion, by the addition of potassium salt to the diet, in cases of nephritis in which it had been proved that there was a decreased ability of the kidney to excrete salt.

Selected cases with chronic nephritis were studied in the wards of the hospital. The methods used and the data recorded are exactly the same as those used in the paper[1] previously referred to. In this problem, each case was first studied functionally, and classified. In certain cases, when it had been proved that there was definite inability of the kidney to excrete 10 gm. of added sodium chlorid, the patient was given potassium chlorid. The salt was administered in a single dose of 5 or 10 gm., in 150 c.c. of water at 10 a. m.

In some of the cases there was an apparent increase of the salt excretion following the increased potassium chlorid intake; in other cases no apparent effect was produced.

---

* Submitted for publication April 7, 1915.

* From the Department of Medicine, Harvard University and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Frothingham, C., and Smillie, W. G.: A Study of Different Nitrogenous Diets in Chronic Nephritis, The Archives Int. Med., 1915, xv, 204.

2. Widal: Mouvement Med., 1913, i, 1.

3. Bunge: Ztschr. f. Biol., 1873, ix, 104.

Four typical tables will be given.

CASE 1 (1170).—This was classified clinically as of chronic nephritis, arteriosclerosis and hypertension. Functionally, there was moderate inability to excrete salt, with practically normal nitrogen excretion. On the 17th, 5 gm. of potassium chlorid were given. No increase of salt excretion occurred. No ill effects were produced. Results are given in Table 1.

TABLE 1.—RESULTS OF TEST IN CASE 1 (1170)

Date	Fluid Intake c.c.	Urine		Nitrogen		Chlorid		Mg. N per 100 c.c. Blood	Per Cent. Phthalein in 2 Hrs.	Blood Pressure
		24° Am. c.c.	Sp. Gr.	Intake Gm.	Output Gm.	Intake Gm.	Output Gm.			
May 9	.....	1,880	1.016	11.2	12.6	4.0	14.0	34.2	50	230-130
May 10	.....	745	1.022	11.2	10.6	4.0	3.2			
May 11	.....	890	1.021	11.2	12.4	4.0	3.4			
						NaCl 10 gm.				
May 12	.....	1,515	1.020	11.2	12.2	14.0	9.5			
May 13	.....	1,530	1.014	11.2	12.2	4.0	5.1			
				Urea 20 gm.						
May 14	.....	1,530	1.015	21.2	16.4	4.0	3.0			
May 15	.....	1,160	1.017	11.2	12.8	4.0	1.5			
May 16	.....	1,340	1.017	11.2	14.7	4.0	3.6	.....	59	
						KCl 5				
May 17	700	1,060	1.016	11.2	10.6	9.0	3.5	28.5		
May 18	1,310	840	1.020	11.2	10.3	4.0	2.8			
May 19	1,480	980	1.020	11.2	11.5	4.0	2.8			

CASE 2 (1072).—This was classified clinically as of chronic nephritis with hypertension. Functionally there was marked inability to excrete salt, and moderate inability to excrete nitrogen. On May 5, 5 gm. of potassium chlorid were given, which was followed by an immediate increase in the chlorid output. No ill effects were produced. Results are given in Table 2.

TABLE 2.—RESULTS OF TEST IN CASE 2 (1072)

Date	Fluid Intake c.c.	Urine		Nitrogen		Chlorid		Mg. N per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24° Am. c.c.	Sp. Gr.	Intake Gm.	Output Gm.	Intake Gm.	Output Gm.			
April 16	1,100	1,480	1.015	10.7	3.1	4.0	7.2	.....	.....	190-100
April 17	1,300	1,100	1.010	9.7	3.0	3.0	1.2	31.8	60	
						NaCl 10 gm.				
April 18	950	840	1.015	10.7	6.3	14.0	4.0	.....	.....	200-110
April 19	1,300	1,180	1.009	8.8	3.5	3.0	2.7			
				Urea 20 gm.						
April 20	1,300	2,400	1.010	18.7	8.2	4.0	6.7	.....	.....	210-112
April 21	1,500	1,810	1.010	10.7	8.0	4.0	3.2			
May 3	1,350	1,460	1.008	4.0	4.8	4.0	1.5			
May 4	1,200	1,090	1.010	4 0	4.6	4.0	1.9	.....	.....	170- 98
						KCl 5				
May 5	1,100	1,355	1.010	4.0	2.8	9.0	7.2	23.7	51	

Case 3 (1154).—This was classified clinically as of chronic nephritis, with albuminuric retinitis and hypertension. Functionally there was a marked inability to excrete added sodium chlorid, with slight inability to excrete added urea. On May 17, 10 gm. of potassium chlorid were added to the diet. No increase of salt excretion occurred. No ill effects were produced. Results are shown in Table 3.

Case 4 (1097).—This was classified clinically as of chronic nephritis with hypertension. Functionally there was a moderate inability to excrete added sodium chlorid, and slight inability to excrete added urea. Ten grams of potassium chlorid were administered on May 8. This was followed by a definite increase in the salt excretion. No ill effects were noted. Results are shown in Table 4.

In two of the cases, additional potassium chlorid produced no increase of chlorid excretion; in two cases there was a definite increase of chlorid excretion. In none of these cases were there any ill effects from the potassium chlorid.

The next case reported was similar both clinically and functionally to those already given.

Case 5 (1158).—A Russian Jewess, aged 42, married, entered the hospital May 5, 1914, complaining of headache and dizziness of a duration of two or three months.

Family History.—The patient's husband and eleven children were living and well. She had had three miscarriages. There was no history of cancer, heart or kidney disease in the family.

Her habit has been to use a moderate amount of tea and coffee for years. Venereal disease is denied.

Past History.—The patient had scarlet fever in childhood; otherwise her general health has been very good. There has been slight dyspnea on exertion for the past few years. Nocturia four or five times for several years has been a troublesome symptom.

Present Illness.—Headaches have been frequent and severe for the past two or three months. Before this time headaches were rare. These headaches are now present two or three days of the week. There has been some dizziness for the past six weeks. A slight puffiness about the face and eyes was noted a month ago. About two weeks ago there was some nausea and vomiting.

Physical Examination.—There is a definite hypertrophy of the heart, the left border being 13 cm. to the left of the midsternum in the sixth space.

A blowing systolic murmur was present, best heard over the sternum. There is no edema of the face or extremities. The fundi of the eyes are normal. Blood pressure, systolic 245, diastolic 120. Physical examination otherwise is negative.

The urine showed a large trace of albumin, with granular casts and many white cells, but no blood. Phthalein test, two hours, 59 per cent.; nonprotein nitrogen, 31.1 mg. per 100 c.c. of blood.

Clinical Diagnosis.—Chronic interstitial nephritis, hypertrophy of the heart, hypertension. Functional tests of the kidney, begun May 16, were not entirely satisfactory because of slight inability to control the urethral sphincter. The added sodium chlorid was poorly excreted; the added nitrogen was excreted fairly well. On May 24, 10 gm. of potassium chlorid were given at 10 a. m. Several hours after taking the salt the patient complained of weakness, abdominal distress and precordial pain. At 5 p. m. she was somewhat cyanotic, markedly prostrated, with regular, rather weak pulse; rate 80. There was considerable abdominal distress and vomiting during the night. At 6 a. m. on

TABLE 3.—Results of Test in Case 3 (1154)

Date	Fluid Intake c.c	Urine		Nitrogen		Chlorid		Mg. N per 100 c.c. Blood	Per Cent. Phthalein	Blood Pressure
		24° Am. c.c.	Sp. Gr.	Intake Gm.	Output Gm.	Intake Gm.	Output Gm.			
May 8	2,500	2,254	1.010	11.2	13.0	4.0	10.7	30.9	45	
May 9	1,950	1,305	1.013	11.2	9.1	4.0	5.8	.....	.....	220-140
May 10	1,350	1,020	1.021	11.2	10.3	4.0 NaCl 10 gm.	5.3			
May 11	1,500	765	1.025	11.2	6.5	14.0	2.4			
May 12	1,450	940	1.026	9.9	10.9	4.0	3.6	.....	.....	260-160
May 13	1,800	600	1.016	11.2 Urea 20 gm.	7.1	4.0	1.1	.....	.....	255-155
May 14	2,700	3,300	1.010	20.7	19.1	4.0	4.3	.....	60	230-150
May 15	2,100	940	1.020	9.9	9.3	4.0	1.4			
May 16	1,900	1,830	1.017	9.7	9.3	4.0 KCl 10 gm.	0.9			
May 17	2,100	1,150	1.011	8.7	7.3	14.0	2.7	.....	.....	220-150
May 18	1,700	1,330	1.013	20.0	8.8	2.0	4.9			
May 19	1,650	1,245	1.013	22.5	12.0	4.0	2 8	35.1		

TABLE 4.—Results of Test in Case 4 (1097)

Date	Fluid Intake c.c.	Urine		Nitrogen		Chlorid		Mg. N per 100 c.c. Blood	Per Cent. Phthalein in 2 Hrs.	Blood Pressure
		24° Am. c.c.	Sp. Gr.	Intake Gm.	Output Gm.	Intake Gm.	Output Gm.			
April 30	1,200	1,030	1.019	6 1	8.5	6.0 NaCl 10 gm.	4.0			
May 1	1,500	890	1.022	6.0	7.7	16.0	4.5			
May 2	1,250	550+	1.018	6.0	3.5+	6.0	7.7+	.....	.....	195-110
May 3	1,500	700	1.019	6.0 Urea 20 gm.	4.7	6.0	5.5			
May 4	1,200	1,465	1.017	6.0	12.5	6.0	9.6	.....	.....	180-100
May 5	1,500	410+	1.020	6.0	2.6+	6.0	3.2+	.....	51	
May 6	1,300	Lost	Lost	6.0	Lost	6.0	Lost			
May 7	1,300	840	1.018	11.2	6.4	4.0 KCl 10 gm.	5.2			
May 8	1,500	1,465	1.017	11.2	13.1	14.0	10.2	32.2	.....	190- 85
May 9	1,500	980	1.020	11.2	7.0	4.0	5.8			
May 10	1,200	1,165	1.022	11.2	13.4	4.0	5.2			
May 11	1,550	950	1.022	11.2	10.7	4.0	5.0	.....	51	200-100
May 12	1,250	1,310	1.013	11.2	8.0	4.0	3.7			

the 25th there was a sudden attack of intense cyanosis and marked prostration. There was a diminution in the amount of urine. There had been only a few blood cells in the urine but on the 26th a marked hemoglobinuria appeared. The nonprotein nitrogen in the blood had risen to 84 mg. per 100 c.c. The blood serum showed a definite hemoglobinemia. The spectroscope showed absence of methemoglobin.

TABLE 5.—Results of Test in Case 5 (1158)

Date	Fluid Intake c.c.	Urine		Nitrogen		Chlorid		Mg. N per 100 c.c. Blood	Per Cent. Phthalein 2^h 10'	Blood Pressure
		24^h Am. c.c.	Sp. Gr.	Intake Gm	Output Gm.	Intake Gm.	Output Gm.			
May 16	1,495	960	1.016	6.0	6.4	16.0 NaCl 10 gm.	2.2			
May 17	1,500	595	1.015	6.0	4.5	6.0	1.6	.....	.....	180-95
May 18	1,506	895	.....	6.0	.....	6.0				
May 19	1,675	400+	1.014	7.3	2.6+	4.0	0.76+	.....	52	
May 20	1,280	1,350	1.014	Urea 20 gm. 20.0	10.1	4.0	2.5			
May 21	1,330	1,385	1.012	7.0	8.0	3.5	2.3	.....	.....	170-85
May 22	1,310	440+	.....	7.9	.....	3.5				
May 23	590	1,460	1.011	6.3	8.9	3.5	2.2			
May 24	1,635	300+	1.016	5.4	.....	KCl 10 gm.	0.5	.....	.....	184-94
May 25	795	55+	.....	0	?	0	?			
May 26	1,265	408	1.013	0.1	2.5	0	0.4	84.0		
May 27	1,400	310	1.012	0.0	1.9	0	0.3			
May 28	1,350	795	1.012	0.1	5.6	0	0.6	.....	.....	168-85
May 29	1,730	800	1.013	8.0	4.8	3.5	1.4			
May 30	1,760	775+	1.012	5.5	5.3	2.0	0.9	.....	.....	160-75
May 31	1,980	1,280	1.011	5.2	7.0	2.0	1.3			
June 1	1,630	1,200	1.011	8.1	7.2	3.5	1.7			
June 2	1,760	1,275	1.013	7.0	7.2	3.5	1.5			
June 3	1,650	1,700	1.011	8.1	10.9	3.5	1.8			
June 4	1,860	950	1.011	7.5	5.4	3.5	1.1	.....	.....	150-75
June 5	1,910	1,525	1.009	9.8	7.0	4.0	1.5			
June 6	1,810	1,205	1.009	10.5	5.6	4.0	1.2			
June 7	1,560	1,750	1.012	10.0	7.3	4.0	2.1	78.8		
June 20	.....	.....	.....	.....	.....	.....	.....	66.2		
July 1	.....	.....	.....	.....	.....	.....	.....	48.0		
July 4	.....	.....	.....	.....	.....	.....	.....	.....	32	120-58

There was a temperature of 100.8 on the 26th, with an increase in pulse-rate to 98. The temperature and pulse remained elevated for two days.

The symptoms were so severe and resembled so closely those of potassium chlorate poisoning, that at once the question arose as to whether a mistake had been made in the salt given. This was carefully checked and it was soon

proved that the salt given was potassium chlorid. This was substantiated by entire absence of methemoglobin formation. The patient slowly improved and returned to her former condition about June 10. Hemoglobinuria disappeared June 4 and blood cells were gone from the urine June 12. Nonprotein blood nitrogen on the 7th was 78.8 mg., falling to 48.0 on July 4. Throughout her stay in the hospital the blood pressure continued to fall, reaching 120-58 on discharge. She left the hospital with entire relief from headache and dizziness.

This case suggested to us that potassium chlorid in a dose which was harmless in normal individuals might be injurious in nephritis, and since the chlorin ion is devoid of action, that the poisoning must be due either to the action of the potassium ion, or to the "salt action." Since the "salt action" of sodium chlorid and potassium chlorid is the same, and since the patient did not react adversely to 10 gm. sodium chlorid, it seemed probable that the poisoning was due to the potassium ion.

The chief action of potassium in experimental[4] work, is a depression of the heart. There is at first, as a rule, an acceleration of the pulse, then the pulse becomes weaker and slower, and fall in the blood pressure occurs. Bunge[5] has shown that some classes of people—Irish laborers and certain African tribes—have an intake of 50 gm. potassium chlorid a day. The absence of effect on the heart is due to the rapid excretion of the salt by the kidney. Dr. Reid Hunt, in an unpublished experiment, demonstrated that potassium salts in extraordinarily small amounts, produce death in guinea-pigs with the kidneys removed. The guinea-pigs when in normal condition, were injected with various potassium salts without ill effect, for the kidneys excreted the salt so rapidly that the concentration necessary to kill the animal was not reached. With the kidneys removed, much smaller doses of potassium killed the animal at once. Death was probably due to the action of the potassium ion on the heart. He calculated that a man who took a large portion of his food as potatoes, for example an Irish peasant, would have an intake of 10 times the fatal dose of potassium in a day. Were it not for the fact that potassium salts are so rapidly excreted by the kidneys, the effects might be very serious.

Experiments were now made in an attempt to correlate previous laboratory findings and our clinical experience with potassium poisoning in nephritis. Rabbits were given nephritis with uranium nitrate. The degree of nephritis was estimated by frequent blood nitrogen examinations. The same data were kept on rabbits as had been recorded in our patients, with the exception of the specific gravity of the urine, and blood pressure. The rabbits were given a large dose of

4. Macht: Bull. Johns Hopkins Hosp., 1914, xxv, 278.
5. Bunge: Arch. f. d. ges. Physiol., 1871, iv, 235.

potassium chlorid by mouth while in a normal condition. Uranium nitrate was then given subcutaneously to produce nephritis, and varying doses of potassium chlorid were added to the diet at different periods of the disease. A few typical protocols will be given.

Experiment 1, Rabbit 974.—The animal was given 3 gm. of potassium chlorid in 50 c.c. of water, with rapid excretion of the salt (4 gm. in 50 c.c. of water sometimes caused death in the hot summer). A moderate nephritis was then produced by uranium nitrate. The blood nitrogen rose gradually. The animal was strong and showed no marked symptoms of illness. On the 21st, when the nonprotein blood nitrogen reached 118 mg., one gm. of potassium chlorid was given in 50 c.c. of water. The animal died within fifteen minutes. Necropsy showed typical lesions of acute uranium nephritis (Table 6).

TABLE 6.—Results of Test on Rabbit 974, Experiment 1

Date	Fluid Intake c.c.	Urine c.c.	Nitrogen		Salt		Blood Nitrogen mg. per 100 c.c.	Uranium Nitrate Mg.	Weight Gm.	Remarks
			Intake Gm.	Output Gm.	Intake Gm.	Output Gm.				
Sept. 16	210	150	0.7	1.4	0.15	0.13	.....	....	1,800	
Sept. 17	245	190	0.7	0.78	3.1	2.3	29.2	....	.....	3 gm. KCl
Sept. 18	140	130	0.7	0.59	0.11	0.29	23.7	2		
Sept. 19	200	100	0.7	0.43	0.15	0.12	25.8			
Sept. 20	80	20	0.4	?	0.05	?	52.0			
Sept. 21	50	... Died	.....	.....	1.0	.....	118.0	....	1,840	1 gm. KCl

TABLE 7.—Results of Test on Rabbit 958, Experiment 2

Date	Fluid Intake c.c.	Urine c.c.	Nitrogen		Salt		Blood Nitrogen mg. per 100 c.c.	Uranium Nitrate Mg.	Weight Gm.	Remarks
			Intake Gm.	Output Gm.	Intake Gm.	Output Gm.				
July 20	150	110	0.7	0.55	0.15	0.35				
July 21	200	210	0.7	0.32	3.15	1.50	22.9	....	.....	3 gm. KCl
July 22	200	180	0.7	0.56	0.15	0.52	.....	....	1,850	
July 23	200	60	0.55	0.20	0.15	0.20	.....	2		
July 24	190	154	0.55	0.48	0.15	0.11	38.2			
July 25	200	55	0.30	0.20	0.15	0.09				
July 26	30	48	0.14	0.25	0.04	0.07				
July 27	170	58	0.08	0.15	2.10	0.52	105.6	....	.....	2 gm. NaCl
July 28	140	68	0.40	0.17	0.10	0.39	.....	....	1,800	
July 29	50	... Died	.....	.....	1.0	.....	140.0	....	.....	1 gm. KCl

Experiment 2, Rabbit 958.—The rabbit was given 3 gm. of potassium chlorid, with rapid excretion of the salt. Nephritis was produced with uranium nitrate. When the nonprotein blood nitrogen reached 100 mg., 2 gm. of sodium chlorid

were added to the diet. No ill effects were produced, though there was poor excretion of the salt. Two days later 1 gm. of potassium chlorid was given, with immediate death of the animal. There were no symptoms of weakness nor illness before the potassium chlorid was given. Necropsy showed characteristic lesions of acute nephritis. This experiment suggests that death is not due to "salt action," since the "salt action" of sodium and potassium chlorid is the same.

An attempt was next made to produce a moderate nephritis with repeated injection of uranium, adding to the daily diet small amounts of potassium chlorid.

TABLE 8.—Results of Test on Rabbit 975, Experiment 3

Date	Fluid Intake c.c.	Urine c.c.	Nitrogen		Salt		Blood Nitrogen mg. per 100 c.c.	Uranium Nitrate Mg.	Weight Gm.	Remarks
			Intake Gm.	Output Gm.	Intake Gm.	Output Gm.				
Sept. 16	20	75	0.7	1.1	0.15	0.08	.....	....	2,040	
Sept. 17	150	190	0.1	0.72	4.07	2.8	32.8	....	.....	4 gm. KCl
Sept. 18	120	120	0.7	0.45	0.15	0.32	34.3	2	.....	
Sept. 19	50	38	0.1	0.59	0.02	0.05	33.9			
Sept. 29	...	...	.....	.....	.....	.....	.....	4		
Sept. 30	50	155	0.65	0.56	0.62	0.45	28.4	....	1,920	0.5 gm. KCl
Oct. 1	50	130	0.55	0.48	0.62	0.49	36.7	....	.....	0.5 gm. KCl
Oct. 2	50	105	0.40	0.80	0.63	0.51	53.2	....	1,860	0.5 gm. KCl
Oct. 3	50	150	0.55	.....	0.65	0.69	.....	....	.....	0.5 gm. KCl
Oct. 4	50	85	0.55	0.27	0.65	0.48	60.8	....	.....	0.5 gm. KCl
Oct. 5	50	150	0.70	.....	0.63	0.70	.....	6	1,770	0.5 gm. KCl
Oct. 6	50	150	0.35	0.70	0.60	0.64	58.2	....	.....	0.5 gm. KCl
Oct. 7	50	120	0.3	.....	0.60	0.56	.....	....	.....	0.5 gm. KCl
Oct. 8	50	100	0.55	0.57	0.58	0.45	68.4	....	.....	0.5 gm. KCl
Oct. 9	50	60	0.50	0.14	0.60	0.38	.....	....	.....	0.5 gm. KCl
Oct. 10	50	140	0.60	0.49	0.55	0.82	.....	....	.....	0.5 gm. KCl
Oct. 11	50	140	0.60	0.48	0.60	0.63	54.6	....	1,760	0.5 gm. KCl
Oct. 12	50	180	0.55	.....	1.13	1.20	.....	....	.....	1 gm. KCl
Oct. 13	50	240	0.12 Recovered	.....	1.15	1.1	57.9	....	.....	1 gm. KCl

Experiment 3, Rabbit 975.—Four gm. of potassium chlorid were readily excreted on the 19th. Two mg. of uranium nitrate gave no increase in nonprotein blood nitrogen and the data are omitted. On the 29th four mg. of uranium nitrate were given, with moderate gradual increase of blood nitrogen. Though the nonprotein blood nitrogen rose to 60 mg. per 100 c.c., potassium chlorid was readily excreted and no symptoms were evident. On October 5, 6 mg. of uranium nitrate were given. The nonprotein blood nitrogen rose almost to 70 mg., but the potassium chlorid was well excreted and the animal recovered.

Experiment 4.—This experiment is similar to Experiment 3. Moderate nephritis was produced by repeated injections of uranium nitrate, and potassium chlorid was given at various stages of the disease. The salt was well excreted until the nonprotein blood nitrogen became 100 mg. In this case as in the others, 1 gm. of the salt caused sudden death.

TABLE 9.—Results of Test on Rabbit 978, Experiment 4

Date	Fluid Intake c.c.	Urine c.c.	Nitrogen		Salt		Blood Nitrogen mg. per 100 c.c.	Uranium Nitrate Mg.	Weight Gm.	Remarks
			Intake Gm.	Output Gm.	Intake Gm.	Output Gm.				
Sept. 24	200	80	0.7	0.8	0.15	0.22	.....	....	2,260	
Sept. 25	310	280	0.68	1.0	4.1	3.4	23.8	....	.....	4 gm. KCl
Sept. 26	240	180	0.7	0.87	0.15	0.26				
Sept. 27	200	125	0.7	0.86	0.13	0.05	23.1	2		
Sept. 28	245	170	0.7	0.88	0.13	0.12	26.5	....	2,260	
Sept. 29	270	210	0.40	0.60	1.11	1.07	28.2	....	.....	1 gm. KCl
Sept. 30	140	130	0.21	0.54	0.08	0.36	25.4	....	2,230	
Oct. 1	125	130	0.30	0.47	0.07	.....	36.4	3		
Oct. 2	85	90	0.10	0.57	0.03	0.27	36.2	....	2,160	
Oct. 3	120	100	0.50	.....	0.07	0.17	68.0			
Oct. 4	140	85	0.70	0.85	0.06	0.07				
Oct. 5	170	110	0.50	.....	1.1	0.47	57.2	5	2,100	1 gm. KCl
Oct. 6	80	75	0.10	0.42	0.03	0.30				
Oct. 7	100	140	0.10	.....	1.04	0.74	75.6	....	.....	1 gm. KCl
Oct. 8	140	150	0.15	1.0	1.07	0.80				
Oct. 9	180	68	0.10	0.38	0.10	0.14	.....	....	2,040	
Oct. 10	125	180	0.10	1.0	1.07	0.61	93.8	....	.....	1 gm. KCl
Oct. 11	170	180	0.10	0.88	1.08	0.75	.....	....	.....	1 gm. KCl
Oct. 12	50	...	..... Died	.....	1.0	.....	128.6	....	.....	1 gm KCl

Nine other experiments were carried out with similar results. The four examples given are typical. Frothingham, Fitz,[6] and others who have worked with experimental uranium nephritis have shown that death does not occur in the rabbits until the nonprotein blood nitrogen has reached 150, 200, or even 250 mg. per 100 c.c. Furthermore, the animals as a rule show definite symptoms of disease when death is impending.

For our experiments, as is shown, an attempt was made to produce a moderate nephritis, and to give the potassium chlorid before severe symptoms of the disease developed. In each instance, when the non-

6. Frothingham, C., Fitz, R., Folin, Otto, and Denis, W.: The Relation Between Nonprotein Nitrogen Retention and Phenolsulphonephthalein Excretion in Experimental Uranium Nephritis, The Archives Int. Med., 1913, xii, 245.

protein blood nitrogen reached 100 mg. per 100 c.c. the giving of 1 gm. of potassium chlorid caused immediate death. The reason seems obvious, namely, the salt was absorbed by the gastro-intestinal tract, the kidneys were unable to excrete it, and, as in Hunt's experiments, a concentration was reached in the blood which was poisonous to the heart muscle.

Some of the conditions which were present in the experimental animals were also present in the patient, and it is reasonable to assume that some of her symptoms were due to the action of potassium on the heart muscle.

One symptom complex occurred in the patient which was not present in the experimental animals; namely, hemoglobinemia and hemoglobinuria, with rise in temperature and pulse. The cause of this phenomenon will be made the subject of a subsequent paper.

CONCLUSION

1. Rabbits with uranium nephritis of a degree sufficient to increase the nonprotein blood nitrogen to 100 mg. per 100 c.c., die with great suddenness following ingestions of 1 gm. of potassium chlorid.

2. Their death is not due to "salt action," but is probably due to the action of the potassium ion on the heart muscle.

3. In human beings, potassium chlorid, in doses which have no effect on normal individuals, will cause acute poisoning in individuals with chronic nephritis.

4. This acute poisoning occurs because the salt, which is normally readily absorbed and very rapidly excreted, in nephritis is readily absorbed and not excreted, thus reaching a concentration in the blood which is injurious.

BOOK REVIEWS

ANOCI-ASSOCIATION. By George W. Crile, M.D., Professor of Surgery, School of Medicine, Western Reserve University, Cleveland; and William E. Lower, M.D., Associate Professor of Genito-Urinary Surgery, School of Medicine, Western Reserve University, Cleveland. Cloth, $3 net. Pp. 259, with original illustrations. Philadelphia and London: W. B. Saunders Company, 1914.

Under a strange and forbidding title is concealed a work that may seem out of place in the review pages of a periodical devoted to internal medicine. But internal medicine has many frontiers and on the borderline of surgery the internist should be as much at home as he is in his own special field. In this work are gathered the later results of a study of surgical shock by a facile surgeon and no less facile writer, a keen observer and untiring student who has had the advantage of thorough training in physiological methods and physiological principles. It is not intended to discuss here the facts or conclusions announced. Many details on which the kinetic theory of shock is based have yet to be confirmed. But the book is more than a new presentation of shock. It contains many surgical experiences and suggestions that will repay careful study by all. "The Treatment of Shock and its Prevention through Anoci-Association," by Dr. Crile and Dr. Lower, fills more than half the book and contains much of interest on many borderline subjects, such as abdominal operations, exophthalmic goiter, high and low blood pressure and postoperative morbidity and mortality. Other valuable chapters are included on "Nitrous Oxid Anesthesia," by Agatha Hodgins; "Anoci-Association in Its Relation to the Preoperative and Postoperative Care of Patients," by Samuel L. Ledbetter, Jr. Numerous illustrations add to the value of the work.

DIETETICS: OR FOOD IN HEALTH AND DISEASE. By William Tibbles, LL.D., M.D., L.R.C.P., M.R.C.S., L.S.A. Medical Officer of Health, Fellow of the Royal Institute of Public Health, etc. Octavo, 627 pages. Cloth, $4.00, net. Lea & Febiger, Publishers, Philadelphia and New York, 1914.

With the growing interest in metabolism and nutrition, as well as the desire for greater accuracy of feeding in health and disease, there is a demand for books containing the essential data. The present work finds some well-established competitors, yet it promises to make itself a field. It is well arranged; the various divisions are well balanced. The statements of facts and the discussions of unsettled questions are on the whole accurate and fair. On some points improvements might be made. Thus, the table of heat values of various foods gives the amounts in ounces, but as many diet kitchens are equipped with metric weights it would hasten the wider use of the metric system if amounts were given in grams as well. The discussion of the digestibility and absorption of foods is clear and sufficiently comprehensive and the same may be said of the important subjects of mineral and water metabolism. The consideration of Fletcherism and the work of Chittenden will strike most readers as fair, inclining as it does to the liberal side. There are many useful summaries of dietaries of armies, institutions and trainers. The remarks on alcohol will not please the total abstainer but will probably conduce to temperance. The directions for the treatment of various diseases are such as to be of great value to all. There are some omissions in these sections, as in leaving out the important work of Shaffer and Coleman in typhoid fever. The completeness of the work is shown by the discussion of vitamins though there is internal evidence in a certain unevenness that this chapter was written late. The errors in the spelling of proper names are unduly numerous and the index might be improved. On the whole the work is certain to be useful, and one factor in this is its convenient size and weight.

CONTENTS OF VOLUME XV

APRIL, 1915. NUMBER 4

MAY, 1915. NUMBER 5. PART 1

MAY, 1915. NUMBER 5. PART 2

JUNE, 1915. NUMBER 6

CONTENTS

THE ARCHIVES OF INTERNAL MEDICINE is issued monthly. Two volumes are published annually.

Manuscripts offered for publication and other correspondence relating to the editorial management of THE ARCHIVES should be sent to Dr. Joseph L. Miller, 122 South Michigan Boulevard, Chicago. Communications regarding subscriptions, reprints, etc., should be addressed to THE ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Footnotes and bibliographies should conform to the style of the Index Medicus or to that of the Index-Catalogue of the Surgeon-General's Library. It is specially requested that the titles of articles and the exact date of issues, year, volume and page, be given in each case. Contributors are requested not to furnish bibliographies which are unnecessary, or mere clerical compilations. On receipt of 10 cents the American Medical Association will send a pamphlet entitled "Suggestions to Medical Authors," containing suggestions to authors on the preparation of manuscripts, rules for footnotes and bibliographies and a list of several hundred medical periodicals of the world with approved abbreviations of each.

Authors will receive one hundred reprints free; additional copies may be obtained at cost.

The domestic subscription price per year of two volumes is $4.00; Canadian rate $4.25; foreign rate $4.40 (18 shillings, 18 marks, 22 francs); including postage. Single copies 50c postpaid.

Make checks, etc., payable to the AMERICAN MEDICAL ASSOCIATION.